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ARCHIVES OF SURGERY

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IRRADIATION OF MAMMARY CANCER, WITH SPECIAL REFERENCE TO MEASURED TISSUE DOSAGE *

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Carcinoma situated in the breast has certain physical advantages for treatment by irradiation. The mammary gland is superficial enough so that any tumor in its depth may receive a considerable percentage of the energy from external sources of radiation. The accessibility of the breast permits a reasonably correct measurement of the tumor, an accurate estimation of the dosage and the proper implantation of radioactive foci. The reactionary phenomena following irradiation of the breast are of little moment and are seldom complicated by sloughing and infection, which are frequently present in tumors of the respiratory, genito-urinary and alimentary canals. The loss of mammary function is relatively unimportant to patients with carcinoma of the breast, since their average age is slightly over 50 years. Irradiation of mammary cancer does not contraindicate subsequent mastectomy; therefore the opportunity is afforded to apply various methods of irradiation, to amputate the breast, to study critically the histologic changes produced, and in certain cases to employ irradiation in proper dosage as the sole method of treatment.

Opposed to these advantages are certain undeniable handicaps to successful irradiation in cancer of the breast. The majority of mammary cancers are relatively radioresistant. The thick fat envelop of the breast is an extremely poor reactive tissue bed, which contributes little in the way of productive inflammation and fibrosis toward the destruction of carcinoma by irradiation. The delicate and moist skin of the axilla and sulcus of the breast will not tolerate much external irradiation. Many breast cancers metastasize widely before any treatment has been

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* From the Memorial Hospital for Cancer and Allied Diseases.

* Read before the Section on Radiology at the Eighty-First Annual Session of the American Medical Association, Detroit, June 25, 1930.

instituted; in such an event it is just as important (although more difficult) to destroy the metastatic carcinoma as it is the primary lesion.

We shall trace the evolution of methods of radiation for mammary cancer at the Memorial Hospital through the periods devoted to external irradiation only, the interstitial use of glass-filtered radon seeds, the employment of puncture by platinum-filtered radium needles, to the present mode of external irradiation followed by the interstitial deposition of gold radon seeds. Since July, 1929, 130 patients with primary operable and inoperable carcinomas of the breast have been treated by measured tissue doses of irradiation, expressed in terms of skin erythema units. The patients were divided into various groups; some were treated by roentgen rays only, others by external irradiation with the 4 Gm. radium element pack, others by interstitial irradiation alone, and still others by various combinations of external and interstitial irradiation. In the primary operable cases, most of the breasts were removed, with the axillary contents, at variable intervals after the completion of treatment, and multiple and whole sections of the breast were subjected to careful microscopic study. This material afforded opportunities to judge the radiosensitivity of carcinomas of the breast in terms of biologic units of measurement, and finally to study the tissue changes produced by the different methods of irradiation.

Until recently, trial of the curative power of roentgen rays and radium had been limited largely to recurrent and primary inoperable carcinomas of the breast, which accounts to some extent for the slow progress in the methods of radiation therapy for mammary cancer. Although for one reason or another, in the past a considerable number of patients with primary operable carcinoma had been treated by irradiation alone, a carefully measured dosage had not been made, and the significance of histologic changes could not be evaluated. This information was obtained in the present study. Therefore we may generalize by saying that there is no phase or variety of this disease, operable, inoperable, recurrent or prophylactic, in which one may not make use of irradiation on a basis of accurate knowledge of treatment factors.

A. PRIMARY OPERABLE CARCINOMA OF THE BREAST

It is generally recognized that in the beginning cancer of the breast is a local disease, but that it remains localized for a comparatively short period. For prognosis, it is insufficient to group primary operable mammary cancers together without statements relative to the age of the patient, the presence of lactation, the rate of growth of the tumor, the size of the primary lesion and the presence or absence of homolateral operable metastases to the axillary lymph nodes. Lee formulated a clinical index of malignancy, based on these factors, which we shall use throughout our tables in lieu of more complete clinical data. Numerical

values are assigned to these various factors; the summation of these figures serves to divide the primary operable carcinomas of the breast into three arbitrary groups: (*a*) slightly malignant (relatively benign), (*b*) moderately malignant and (*c*) highly malignant.

The clinical diagnosis of carcinoma of the breast is seldom wrong, yet when a new nonsurgical method of treatment is under investigation, it is essential, for statistical purposes at least, to confirm the diagnosis

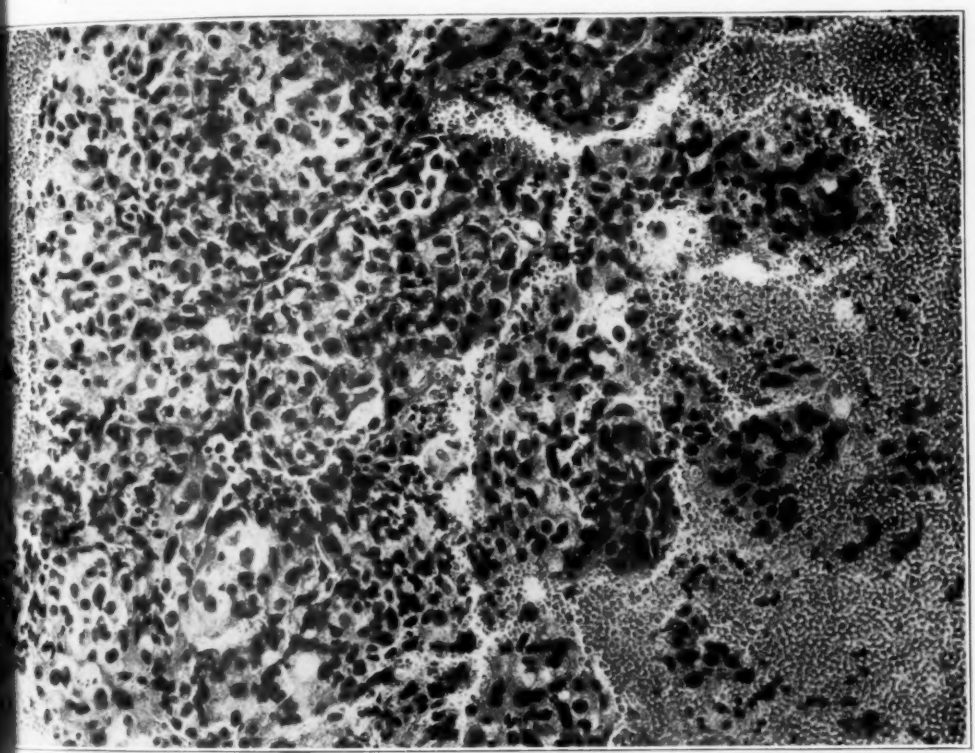

Fig. 1.—Section of a specimen of mammary cancer taken at biopsy by aspiration; method of Martin and Ellis of the Memorial Hospital.

by microscopic examination. In the cases in which subsequent mastectomies are contemplated, preliminary biopsies are unnecessary. When irradiation is the only treatment planned, the biopsy is obtained after external irradiation has been given and before interstitial irradiation has begun. Simple and safe methods of biopsy in use at the Memorial Hospital are the aspiration of these tumors through long, 18 gage needles, such as those perfected by Martin and Ellis, or punch removals of tiny portions of the carcinoma, followed by electrocoagulation of the needle track, as devised by W. J. Hoffman.

METHODS OF IRRADIATION AND SURGICAL INTERVENTION

In the management of primary operable carcinoma of the breast by irradiation and surgical intervention, there are at least seven possible methods.

Surgical Intervention Alone.—The type of radical mastectomy performed at the Memorial Hospital is a modification of the Willy Meyer-Halstead technic. A long, oblique, elliptical incision, encompassing the skin 2½ inches (6.3 cm.) beyond the palpable margins of the tumor, is made from the junction of the pectoral fold with the arm to a point 2 inches (5 cm.) below the costal margin. Both pectoral muscles are removed, and a careful, wide dissection of the fat and fascia underlying the flaps of skin from the midsternal line to the latissumus dorsi is made. As far as is practicable, the dissection of the axilla is carried out from the apex, above and without, downward and inward, along the axillary vein; en masse removal is accomplished of the axillary contents, pectoral muscles, fascia, mammary gland and skin, the dissection ending below with a removal of fascia covering the rectus muscle. Few instances of local recurrence follow this complete operation. Following radical mastectomy, the percentage of survivals for five years without evidence of cancer is practically the same (35 per cent) in the leading surgical clinics of America and Europe. Improvements in operative technic do not promise decided betterment in the end-results. Surgical intervention alone cannot cope satisfactorily with the problem of mammary cancer.

External Irradiation Alone.—Roentgen rays or radium applied at a distance from the breast are only adjuvant measures, preliminary to the more radical procedures of interstitial irradiation or surgical intervention for the primary operable carcinomas. The amount of radiant energy reaching the depths of these tumors of the breast has always been insufficient to produce a lethal effect. As will be seen later, the physical measurement of the dosage delivered by these methods reveals why external irradiation alone can induce only growth restraint without sterilization of the carcinomas (table 7, patients L. R. and E. B.).

Interstitial Irradiation Alone.—The proper intratumoral espacement of radioactive foci in sufficient dosage may destroy the carcinoma, but the method of introducing the radium by puncture is theoretically fraught with the danger of disseminating the carcinoma cells. Furthermore, a slight error in the distribution of the radium in the tumor conceivably might permit certain of the carcinoma cells to survive.

External Plus Interstitial Irradiation.—When these two methods are employed consecutively, the external always precedes the interstitial irradiation. The menace of dissemination of the disease by the interstitial method is presumably lessened by preliminary external irradiation. This is the present procedure of choice for primary inoperable carcinomas of the breast, and when perfected may supplant surgical intervention as the ideal treatment in the primary operable group. By this method, the cosmetic and functional end-results in the breast and axilla are superior to those following surgical intervention. Hitherto, the only primary operable carcinomas of the breast purposely subjected to this treatment have been those that occurred in patients who had intercurrent diseases, such as diabetes, cardiac ailments and tuberculosis of so serious a nature as to contraindicate operative removal. Occasionally, the patient has absolutely refused to sacrifice her breast by amputation, in which circumstance the surgeon has elected the combination of external and interstitial irradiation as the only alternative. Sufficient time has not elapsed or experience accumulated to encourage the routine adoption

of this treatment, but because of our histologic studies following the proper application of this treatment, we are optimistic concerning its possibilities.

Interstitial Irradiation Plus Surgical Intervention.—With the proper dosage and the correct interval before mastectomy, the combination of interstitial irradiation plus operation affords a certain surety of destruction of the primary tumor (table 8). We have never observed any ill effects attributable to this method of treatment, although the theoretic dangers of the dissemination of cancer obtain in the absence of preliminary external irradiation.

External Irradiation Plus Surgical Intervention.—This method has been the usual treatment for primary operable mammary cancer during the last few years at the Memorial Hospital. The percentage of survivals for five year periods, without evidence of cancer is only about 5 per cent better than that by surgical intervention alone. Nevertheless, that preoperative external irradiation is of value is proved by the occasional marked regression in tumors so treated, by the histologic changes produced and by the better clinical end-results.

External and Interstitial Irradiation Plus Surgical Intervention.—We are treating patients with primary operable mammary cancer at present by external irradiation, then by interstitial irradiation followed by radical amputation six weeks or more later. The patients treated by measured tissue doses and by radical surgical intervention have not received postoperative roentgen treatments, as it was decided that the addition of such a procedure might invalidate the end-results of these clinical studies.

PREOPERATIVE EXTERNAL IRRADIATION

An efficient devitalizing dose of irradiation cannot be delivered by external irradiation alone, except in the case of certain unusual anaplastic cancers of the breast. The basis for the use of preoperative external irradiation depends partly on clinical experience and partly on histologic evidence. We have had ample demonstration at the Memorial Hospital that many cases of mammary cancer show a partial regression within from a few days to a few weeks after external irradiation, and that the occasional radiosensitive carcinoma may disappear. This diminution in size is the rule rather than the exception. Tumors become better defined, and in some of our inoperable cases in which fixation to deeper parts had formerly been present, definite mobility has been obtained. In general, the more highly malignant the tumor the greater the radiosensitivity and the more extensive are its clinical evidences of regression. In this manner, irradiation may serve as a therapeutic test of the malignancy of a carcinoma. One does not obtain this regression with such radioresistant tumors as the scirrhous and diffuse duct carcinomas of the breast. Our clinical experiences strongly favor the use of external irradiation prior to interstitial irradiation and operation in the attempt to convert, temporarily at least, a growing tumor into a regressive one.

Until 1920, the only roentgen-ray machines in use at the Memorial Hospital were those of the so-called low voltage type. The whole breast and adjacent regions were divided into four or six areas, each area being treated on successive

or alternate days, until all had been irradiated. In some instances, this type of treatment was given for months, with little or no intermission between cycles. The set-up for delivering the dose was as follows: a peak voltage varying between 120 and 155 kv., 5 ma. of current, from 2 to 4 mm. of aluminum filter, a focal distance of from 8 to 8¾ inches (around 21 cm.) and a treatment time of from three to six minutes. Later the time was lengthened to seven or eight minutes, the target-skin distance increased to 9 or 10 inches (around 23 cm.), but the number of aluminum filters was unchanged. Then, in 1921, the set-up included a peak voltage of 140 kv., 4 ma. of current, a filter of 4 mm. of aluminum, a target-skin distance of 12 inches (30.48 cm.), an exposure of fifteen minutes and an average portal of approximately 300 sq. cm. In 1922, with the same peak voltage of 140 kv., 4 ma. of current, 5 mm. of aluminum filter and a

Fig. 2.—The 4 Gm. radium element pack at the Memorial Hospital.

portal of entry of the same size were used; the target-skin distance was increased to 15 inches (37.54 cm.) and the time to twenty-five minutes. This set-up is still in use, especially for postoperative roentgen treatments over the lower portions of the anterior and lateral area of the chest.

All preoperative roentgen treatments are now given by the high voltage machines with the following factors, 200 kv., 30 ma., 50 cm. target-skin distance, and a filter of 0.5 mm. of copper and 2.5 mm. of aluminum.

The early "pack" for external radium therapy was constructed with a radiating area of 70 sq. cm., and a filter of 0.5 mm. of silver and 1 mm. of brass, which is the filtration equivalent of 2 mm. of brass. The radon pack carried an amount of emanation varying from 1,200 to 2,500 millicuries, and was placed at a distance of 6 cm. from the skin for an average dosage of 12,000 millicurie hours. This applicator has been largely supplanted by the present radium element pack, which contains 4 Gm. of radium. The radium-skin distance is 6 cm. The

filter is 0.3 mm. of platinum and 1.5 mm. of brass. For therapeutic purposes, the average dose is 16,000 milligram hours.

The usual cycle of irradiation of the breast, whether by high voltage roentgen rays or by radium element pack, consists of four exposures, namely, the first two over the breast proper and the last two over the axilla and supraclavicular regions. The first treatment over the breast proper is given in front and the second from the side, thus an additional portal of entry for cross-firing is used, thereby almost doubling the dose to the tumor and its environment. When the breast is small, the treatment by radium element pack can be given over only one area on the breast. It will be noted that the supraclavicular treatment augments the amount of irradiation to the apex of the axilla.

The radium element pack and the high voltage roentgen rays are different in their modes of application and in the results produced. The roentgen rays are more economical when a large number of patients are to be treated, because each dose may be given in from fifteen to sixty minutes. The radium element pack is a single applicator, and requires four hours to deliver a dose when placed at the usual distance of 6 cm. from the skin. This increased time of exposure is probably an advantage, as we shall explain when we consider the time factor.

With increasing filtration and higher voltage, there is a possibility that the effects of the roentgen rays will approximate the results produced by the gamma rays of radium. Under the present circumstances, however, these two closely related forms of radiant energy seem to produce different histologic changes in the carcinomas. In irradiated breasts, Ewing early observed a preponderance of injury and reaction in the connective tissue (mucinous swelling, fragmentation of collagen fibrils, interstitial hemorrhages and vascular changes) from roentgen rays and more direct injury to the tumor cells from radium. He stated that, "roentgen-rays have not yet reached the hardness upon which selective action appears to depend. There may be advantage in combining roentgen-rays and radium in the treatment of tumors."

Ewing's suggestion of the value of combining the two methods of external irradiation has been under trial for several years at the Memorial Hospital. Our experience in the treatment for mammary cancers has afforded clinical verification of the soundness of this theory. It is assumed that this apparent potentiation is due to the different effects of the gamma and roentgen rays on the carcinoma and its tissue bed. Apropos of this clinical observation, Quimby and Pack conducted a series of experiments which showed that the production of skin erythema by a half and half combination of gamma and roentgen rays required a total of 30 per cent more radiant energy than was required when either was employed alone. The result of this experiment cannot be applied to the treatment for cancer, since the cancer as well as the skin may tolerate the increased quantity of irradiation afforded in the delivery of an erythema dose by this combination. As Ewing has

inferred, however, these two agents do not seem to act by a summation of this effect, but chiefly by direct action on the tumor cells in the case of the gamma rays and indirectly by changes in the tissue bed in the case of roentgen rays.

The order of sequence of the radium and roentgen treatments is not an indifferent matter. When the combination is employed, the roentgen treatments should precede the irradiation by the radium element pack (table 12). The reactions in breast tissue following roentgen treatment appear later than do the changes produced in the tumor cells by the gamma rays. Another argument for this order of employment is based on the

TABLE 1.—*Percentage of Variations in Depth Dosage with Variation in the Size of the Field**

	Size of Field, Sq. Cm.					
Depth, Cm.	30	50	75	100	200	400
0	100	100	100	100	100	100
5	57	61	64	67	72	75
10	26	28	31	33	38	41

* The dose on the skin was constant at 100 per cent S. E. D.

TABLE 2.—*Depth Dose if the Skin Always Receives a Dose that Gives S. E. D. for a 100 sq. cm. Field*

	Size of Field, Sq. Cm.					
Depth, Cm.	30	50	75	100	200	400
0	90	94	97	100	104	106
5	51	57	62	67	75	80
10	23	26	32	33	40	44

experience gained in treating patients with malignant neoplasms in other locations, in which radium has proved successful after the roentgen rays have failed, and in which roentgen therapy has failed after radium treatments have been insufficient.

Particularly when the roentgen rays are employed, a large area of skin is exposed at each treatment. In the average case, this area measures 15 by 15 cm. The reasons for using such a large area are numerous. The first is that the entire diseased tissue and the surrounding normal tissues may be fully irradiated, for if one limits irradiation only to the palpable tumor, in some instances, an outlying nonpalpable cancer may escape control. Another reason for selecting large areas is that the larger the skin surface, the greater will be the depth dose because of the augmentation of this dose by the scattered radiation produced. In small breasts, this extra amount of scattered irradiation is negligible because of the small skin portals employed. The variations in dosage caused by this factor are shown in table 1.

The tray is a small external applicator for radium therapy; it contains radon at a distance of 3 cm. from the skin. The radiating surface measures 24 sq. cm. and the filter is 2 mm. of brass. The average dosage is 3,000 millicurie hours. This applicator is used chiefly for single, small, fixed recurrent nodules of carcinoma, although occasionally it is employed as a preoperative measure for small mammary cancers situated superficially at the periphery of the breast (table 11, patient, N. J.).

In light complexioned patients, especially in those with reddish hair and ruddy complexions, a skin erythema develops more readily than in brunettes. In treating the former, a dosage less than the average should be planned and given, or damage to the skin may follow. On the other hand, an erythema develops less readily in anemic and undernourished persons than in the average patient.

THE TIME FACTOR IN PREOPERATIVE IRRADIATION

Preoperative irradiation delays operation. Objection may be raised to such delay on the ground that it may permit extension of the disease, but it appears probable that carcinoma subjected to irradiation even by external methods alone is less likely to metastasize. Moreover, we believe that when a tumor and its drainage areas have been properly irradiated by roentgen rays or the radium element pack, neoplastic cells dislodged during the subsequent operation are less likely to remain viable, and thus the menace of recurrence is diminished. After interstitial irradiation, the interval of time before mastectomy is still greater, because of the persistent radium reaction. The radon deposited within the breast has an exponential rate of decay, less than 6 per cent remaining at the end of thirty days. The irradiation, therefore, by this interstitial method is continuous, but with diminishing intensity.

With regard to the factor of time, there are three principal methods for irradiating mammary cancer.

The Single Efficient Killing Dose.—This dose cannot be delivered by external irradiation, because the skin of the breast will not tolerate an exposure of a sufficient amount to deliver a sterilizing dose to the depths of the tumor. Interstitial irradiation is the only method known at present that furnishes sufficient intensity to destroy the average cancer of the breast.

The Prolonged Single Treatment by External Irradiation.—The principle of this method was established by Régaud at the Curie Institute of the University of Paris. It is generally accepted that in the course of its existence, a cell or a line of cells (cancer cells especially) pass through alternating phases of radiosensitivity and radioresistance. The cells are particularly radioresistant when they have been in a state of

repose or rest for a long time. They are most sensitive to the action of radium or roentgen rays when they are in a state of mitosis or indirect cell division (law of Bergonié and Tribondeau). A short treatment, therefore, would destroy only the cancer cells that are dividing at that time; it spares the others. As the mitotic cycle continues, the various resting cells divide and thereby come under the influence of continuous irradiation. In the treatment for mammary cancer at the Memorial Hospital we have not applied this form of irradiation. Part of the superiority of the radium element pack may be attributed to the fact that the time consumed in treatment is from four to twenty times as long as when the roentgen rays are used. The radon deposited in gold seeds within the tumor is constantly active for twenty-four hours daily, so the advantage of the interstitial method may be due to its continuous action as well as to the intensity of the irradiation. The time of administering a dose of irradiation may vary within wide limits without modifying the degree of tissue reaction or tumor response, providing the treatment does not consume a period equivalent to the life cycle of the normal or cancer cell. Comparative studies on the efficacy of different intensities of radiation in the treatment for cancer are of value only when the duration of exposure in the one experiment is greater than the life cycle of the cancer cell, and the duration of exposure in the other experiment (i. e., greater intensity) is less than the life cycle of the cancer cell.

Ewing considered the prolonged single exposure by external irradiation as the ideal, selective, nondestructive form of radiation therapy, designed to kill dividing cells and to induce gradual atrophy of the tumor cells, but he admitted that its chief indication is for palliation of advanced inoperable or recurrent cancers.

Fractionated Dosage.—This method should never be used in the treatment for operable carcinoma of the breast. The principle underlying its usage has been defined by Ewing as "the cumulative effect of successive doses delivered upon cells rendered vulnerable by the hyperemia and degeneration excited by previous doses." Fractionated dosage applies only to external sources of radiation; when interstitial irradiation is used, the entire amount of radon is introduced at one time. Fractionated dosage by roentgen rays or radium element pack is often suitable for advanced mammary cancers in which abortive fibrosis and growth restraint rather than a cure are expected. Among the many disadvantages of this method are the severe tissue reaction induced, the prolonged delay if subsequent mastectomy is contemplated, the impaired healing of the operative wound because of the fibrosis and impoverished blood supply, and the acquisition of increased radioresistance by the carcinoma.

The entire radiation therapy should be given within three weeks. A prolongation of this period not only renders the radiation less effective,

but adds the probable complication of acquired radioresistance, which is as important a factor as the tissue dose. In order to appraise the method of irradiation, it is necessary that the time consumed be fairly constant. As a rule eight days are required for the average cycle of roentgen treatments for the breast; the same exposures by the radium pack are given within a ten day limit. External irradiation is preferably followed in a day or two by the introduction of the gold radon seeds into the breast and axilla. The radon thus deposited within the breast continues to irradiate the tumor but with diminishing intensity, so that most of the activity is spent during the ensuing fortnight. There is some question in our minds concerning the relative effectiveness of continuous irradiation by radon with an exponential diminution in intensity, as compared with radium element used interstitially, with a constantly equal intensity during an equivalent continuous period.

THE PHYSICAL PRINCIPLES UNDERLYING THE ESTIMATION OF TISSUE DOSAGE

Any intelligent discussion of the effect of radiation must be based on an estimate of the quantity actually producing the phenomenon. In the case of regression of a tumor mass, whether one considers the effect to be a direct one on the malignant cells or a more or less indirect one due to changes produced in the "tumor bed," it must be conceded that it is the amount of radiation actually delivered in that region that is significant. Moreover, it is evident that all points of an irradiated mass cannot receive the same amount of energy; this is particularly true when interstitial radiation is employed. If tumor regression depends on every point receiving at least a definite amount of energy, then it is necessary to know the quantity delivered at the point that received the minimum. It is evident that for external radiation, a knowledge of the amount leaving the source or falling on the skin is of little value, because the amount delivered at a point within the body varies enormously with the depth below the skin. For example, the notation "so many milliampere-minutes" is the correct expression for the dose of emission, but at a target-skin distance of 50 cm. the tumor may be from 50 to 70 cm. from the source of the roentgen rays, and therefore the amount of radiation it receives may vary from 50 to 100 per cent of the skin dose.

In the case of interstitial radiation, a knowledge of the amount used is not sufficient. One must also know the size and shape of the mass, the distribution of the sources and the manner in which the effect varies with the distances from the sources.

It is customary to call the amount of radiation delivered at a given point in the tissue the "tissue dose" at that point. The tissue dose of a given volume of tumor is estimated according to the point within it

that receives the smallest quantity of energy. At the Memorial Hospital, our unit of quantity of radiation in terms of which all tissue doses are expressed is the threshold erythema dose. This is defined as the amount of radiation which, in 80 per cent of all cases after a single application, will produce a faint bronzing or reddening of the skin in about three weeks, and in the other 20 per cent will produce no visible effect. We grant that this unit is not entirely satisfactory, but we find it the best available at present. Full discussions of its use have been previously published. Although the quantitative basis is the best we have for tissue dosage, the response of the various mammary cancers to this same dosage is qualitative, and we have no absolute biologic unit to express this response. The threshold erythema doses for sources

TABLE 3.—*Depth Doses from External Sources of Irradiation*

	Roentgen Rays		Gamma Rays	
Depth, Cm.	200 kv., 0.5 Cu. Mm., 2.5 Mm. Aluminum Filter, 50 Cm. Target-Skin Distance	140 kv., 4 Mm. Aluminum Filter, 30 Cm. Target-Skin Distance	Radium Element Pack: 0.3 Mm. Platinum, 1.5 Mm. Brass Filter, 50 Sq. Cm. Radiating Surface, 6 Cm. Radium-Skin Distance	Radon Tray: 2 Mm. Brass Filter, 24 Sq. Cm. Radiating Surface, 3 Cm. Radium-Skin Distance
0	100	100	100	100
1	99	91	75	62
3	85	66	51	27
5	67	48	35	13
7	52	36	25	8
10	33	22	16	4
12	25	15	12	
15	17	9	8	

of radium and roentgen rays in use at the hospital have been determined by skin tests on a large number of patients. By means of physical experiments, the percentage of the amount of radiation falling on the skin that arrives at any depth within the tissue has been determined. In treatment for cancer of the breast, the external sources used are roentgen rays of various qualities, the radium element pack and, to a less extent, the radon tray. Table 3 shows the percentage of surface radiation arriving at various depths for these sources.

From this table, if the amount of radiation falling on the skin at each portal is known in terms of the threshold erythema (S. E. D.[1]), and if the depth of the tumor below each portal is also known, the tissue dose from external radiation can be determined at once. Figure 3 and figure 4 represent a transverse cross-section of a breast, showing the irradiation by two radium pack treatments (fig. 3) and two high voltage roentgen treatments (fig. 4). In each case one treatment is from the

1. Hereafter the threshold erythema dose will be expressed by the letters S. E. D. (skin erythema dose).

anterior and the other from the lateral direction. Only within a limited region can more than one erythema dose be delivered in this manner.

In interstitial radiation the problem is not so simple. The interstitial sources used at present at the Memorial Hospital are gold seeds

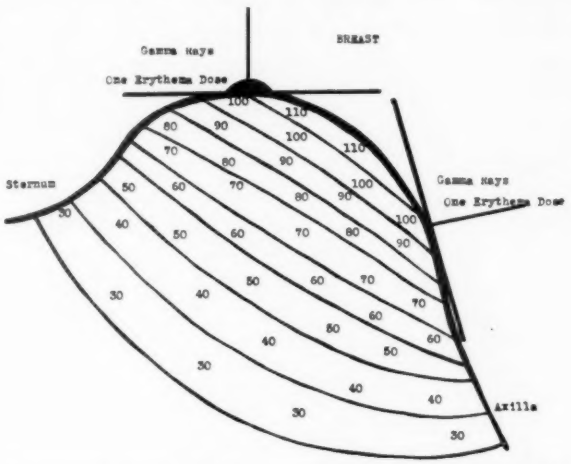

Fig. 3.—Transverse cross-section of a breast showing the depth of doses of irradiation by two radium pack treatments.

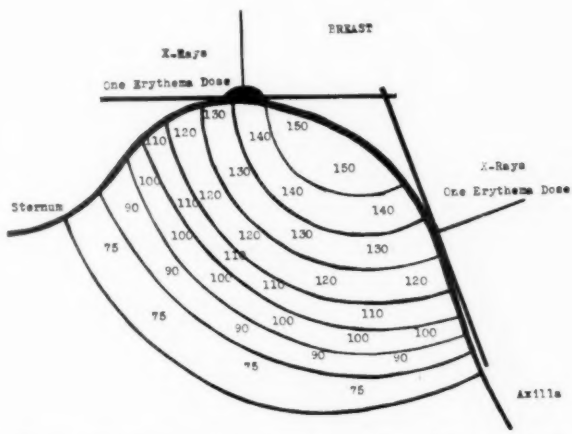

Fig. 4.—Transverse cross-section of a breast showing the depth of doses of irradiation by two high voltage roentgen treatments.

about 4 mm. long, 0.3 mm. in width and thickness and containing from 1 to 3 millicuries of radon. Experimental work previously published makes possible the determination of the percentage of a threshold erythema dose delivered at any distance from any gold seed. The values for a seed of 1 millicurie at different distances are shown in

table 4. For seeds of other strengths, the doses are in the ratio of the millicurie content.

It should be emphasized that the values up to 1.5 are based on much more complete experimental data than those for longer distances. Therefore, in using this table it should be remembered that the data for larger distances may be less accurate than those for shorter ones. With the aid of this table, if one had a chart of any tumor of the breast with the locations and strengths of the seeds that had been implanted, one could measure all their doses from any selected point and find the tissue doses at that point due to the individual seeds.

It is impracticable to do this in actual cases. In the report already referred to, the problem of estimating dosage in masses has been discussed at length, and only the conclusions will be repeated here. We

TABLE 4.—*Tissue Doses at Different Distances from a 1 Millicurie Gold Radon Seed*

Distance, Cm.	Tissue Dose, Percentage, Skin Erythema Dose	Distance, Cm.	Tissue Dose, Percentage, Skin Erythema Dose
0.5	475	1.8	40
0.6	350	2.0	35
0.7	230	2.5	25
0.8	175	3.0	20
0.9	140	3.5	15
1.0	115	4.0	12
1.2	70	4.5	10
1.4	55	5.0	8
1.6	45		

have assumed that it is necessary for every point within the region of the tumor to receive at least a certain minimum dose; and it is the tissue dose for the point receiving the minimum that should be calculated. In a mass in which seeds are uniformly implanted, this point will be on the periphery rather than somewhere inside. For every mass, it is most convenient to consider the sphere of tissue that will just contain it. Of course, in the case of very much elongated or irregular masses, this would include a great deal of normal tissue, and in such types several contiguous or overlapping spheres may be considered. If a definite quantity of radon is to be used in any given sphere, it makes practically no difference in the dose on the periphery whether the radon be concentrated at the center or distributed uniformly within the inner half of the sphere. Therefore, for purposes of approximation of dosage, we consider the radon that is concentrated at the center of the sphere that just contains the mass, and calculate for the minimum the dose at a point on the periphery. Thus a mass 2 by 2 by 3 cm. would be considered a 3 cm. sphere. One millicurie of radon at the center of this (1.5 cm. from the surface) would deliver 50 per cent of an erythema dose on the periphery (table 3). Ten millicuries would

deliver ten times as much, or 500 per cent—5 S. E. D. Therefore, if a mass of this size were treated with 10 millicuries, we should call its tissue dose 5 S. E. D. It is well to keep in mind the approximations used in arriving at this result. The same approximations enter into all the doses quoted in this paper. The fact that the doses are not highly accurate does not lessen the clinical value of the measurements.

For convenience in calculation, we have made a table of doses for different quantities of radon in spheres of different sizes. This is given in table 5. Across the top are indicated the sizes of the masses considered. The first column gives the number of erythema doses, and

TABLE 5.—*Millicuries in Gold Seed Required to Deliver Specified Doses to Masses of Various Diameters*

	Diameter of Mass, Cm.											
	1	1.5	2	2.5	3	3.5	4	4.5	5	6	7	8
Skin Erythema Doses	Number of M.C.											
1	0.2	0.5	0.8	1.5	2	2.4	2.9	3.4	4	5.4	7	9
2	0.4	1.0	1.6	3.0	4	4.8	5.8	6.9	8	11.0	14	18
3	0.6	1.5	2.4	4.5	6	7.2	8.7	10.0	12	16.0	21	27
4	0.8	2.0	3.2	6.0	8	9.6	12.0	14.0	16	22.0	28	36
5	1.0	2.5	4.0	7.5	10	12.0	14.0	17.0	20	27.0	35	45
6	1.2	3.0	4.8	9.0	12	14.0	17.0	20.0	24	32.0	42	54
7	1.4	3.5	5.6	10.0	14	17.0	20.0	24.0	28	38.0	49	63
8	1.6	4.0	6.4	12.0	16	19.0	23.0	27.0	32	43.0	56	72
9	1.8	4.5	7.2	14.0	18	22.0	26.0	31.0	36	49.0	63	81
10	2.0	5.0	8.0	15.0	20	24.0	29.0	34.0	40	54.0	70	90
11	2.2	5.5	8.8	17.0	22	26.0	32.0	37.0	44	59.0	77	99
12	2.4	6.0	9.6	18.0	24	29.0	35.0	41.0	48	65.0	84	108
13	2.6	6.5	10.0	20.0	26	31.0	38.0	44.0	52	70.0	91	117
14	2.8	7.0	12.0	21.0	28	34.0	41.0	48.0	56	76.0	98	126
15	3.0	7.5	13.0	23.0	30	36.0	44.0	51.0	60	81.0	105	135

the others the number of millicuries required to produce these in masses of the sizes considered. For instance, in the column for 3 cm. diameter, we see that 10 millicuries delivers five erythema doses.

It should be mentioned that the data for diameters up to 3 cm. are based directly on measurements of skin erythema doses. Greater distances are calculated from these values on a basis of extensive experimental work in the biophysical laboratory, therefore, they cannot be considered as accurate as the former. However, we have no hesitancy in using them in our calculations of dosage.

THE TECHNIC OF INTERSTITIAL IRRADIATION

Interstitial irradiation as now employed at the Memorial Hospital consists in the distribution of tiny, nonremovable, gold-filtered radon seeds within the substance of the tumor, in the tissues of the breast surrounding the tumor and in the corresponding axilla. In contrast to

the more radical surgical measures, there is no mortality consequent to the introduction of these gold radon seeds; patients with serious cardiac ailments, diabetes, pulmonary tuberculosis, etc., have been treated safely by this method. The possible menace of dissemination of the disease by the method of interstitial irradiation has been considered; we believe that preliminary external irradiation greatly lessens this menace. Thus far we have not observed any untoward results from this procedure, such as early metastases to the bones and the lungs.

Preparatory to inserting the gold radon seeds into the breast, the entire area is prepared carefully as for a major surgical operation. The

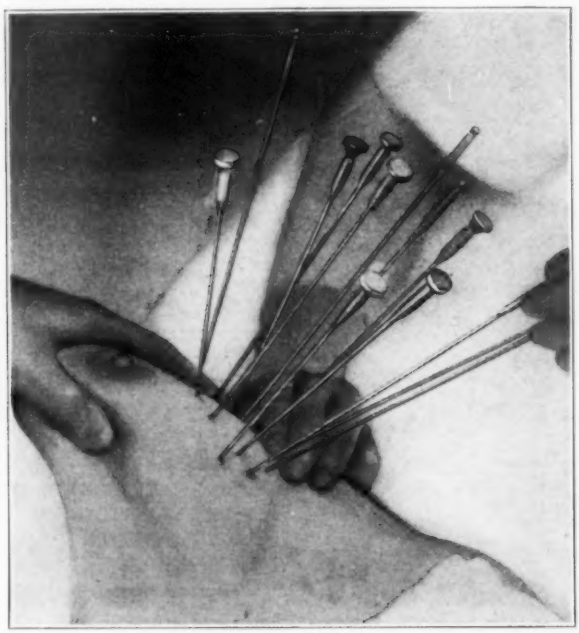

Fig. 5.—Technic of implantation of gold radon seeds in carcinoma of the left breast.

proper use of antisepsis and sterile drapery is essential in order to avoid infection of the cancer. In only one instance among our group of 130 cases did the complication of infection occur; the resultant abscess in the breast was a considerable handicap in the subsequent management of the case and greatly delayed convalescence.

If the tumor is large, nitrogen monoxide anesthesia is used for the very brief time required for the insertion of the seeds. In a few instances, the breast and axilla have been anesthetized by procaine hydrochloride in the outpatient department; this is sufficient when the tumor is small. One word of caution about local anesthesia should be given; if the skin is infiltrated or invaded by the carcinoma,

there exists a definite contraindication to the insertion of procaine hydrochloride solution, for fear of disseminating the disease. The majority of the patients leave the hospital within an hour or two after the insertion of the seeds and remain ambulatory during the entire course of the preoperative treatment.

Each gold radon seed is sterilized in alcohol and placed within a sterile long needle trocar carrying a minute metal plunger for the purpose of dislodging the seed into the depths of the tumor. These needles have sharpened points and are only 1.3 mm. in diameter, in order to cause the least possible trauma. Caution should be exercised that the tubes or seeds are not placed near the skin, otherwise

Fig. 6.—Roentgenogram of the right breast, showing the location of gold radon seeds in an irregular mammary cancer.

they may cause ulceration. Also one should be careful to avoid placing the seeds against a rib or costochondral junction, because of the possibility of injuring the periosteum or cartilage. If the tumor is spherical, the seeds are placed approximately one third of the distance to the center along the various radii, care being taken to place them at all levels.

The placement of gold seeds in tumors less than 4 cm. in diameter is fairly accurate, as the subsequent microscopic examinations reveal, but in the treatment of tumors from 6 to 8 cm. in diameter, unavoidable

errors in technic are constantly present to a variable degree, because it is not humanly possible to distribute tiny gold seeds accurately throughout a mass of these dimensions. As we have stated previously, it makes practically no difference in the dose on the periphery whether the radon is concentrated at the center or distributed uniformly within the inner half of the spherical tumor. Indeed in small spheres, such as single discrete axillary nodes, the entire estimated quantity of radon may be inserted in the center of such a node in a single gold seed focus. The use of a single focus of interstitial irradiation in the center of a mammary cancer, though physically correct, is practically unwise, as the central necrosis thereby induced by such a quantity of radon (i. e., from 30 to 90 millicuries) could not be as easily absorbed as if multiple weaker gold radon seeds were utilized.

THE PROPER TISSUE DOSAGE OF IRRADIATION

What are the advantages of measuring tissue doses of irradiation? The knowledge of the exact amount of radiant energy delivered to the tumor mass gives a rational basis for dosage and eliminates previous empiric methods. The routine estimation and recording of such tissue doses enables one to duplicate good results and to determine the sterilizing dose for various neoplasms. The knowledge of this tissue dose is important in the later microscopic study of the pathologic changes produced.

When external irradiation is employed, all other conditions remaining unchanged, the dose is equal to the product of two factors, namely, the intensity of the rays and the time of irradiation. Without modifying the product, one may vary either the intensity or the time, on the condition that a compensation of the variation of the one by an inverse variation of the other be made. Except for the theoretical advantages of continuous overinterrupted exposures, and the greater selective cancericidal effect of gamma rays over roentgen rays, we have assumed a quantitative equality for these rays and have added the dosage, whenever a combination of these methods was used.

To deliver an efficient dose into a mammary cancer, one must use interstitial irradiation. In the few unusual instances, wherein extremely radiosensitive carcinomas of the breast disappeared completely after external irradiation alone, we have not been content with this immediate result, for in many earlier cases we found that the tumor had not been completely devitalized. We have therefore given supplementary doses of interstitial irradiation based on the original measurements of the tumor.

REPORT OF CASES

CASE 1.—*To illustrate the danger of reliance on external irradiation alone in the treatment for radiosensitive carcinomas of the breast.*

M. F., an Irish widow, aged 66, applied to the Memorial Hospital for treatment on Sept. 20, 1929, complaining of a lump in her right breast. Six children, the oldest of whom was 40 years of age, had been nursed for about eighteen months equally from both breasts. The patient had always been in good health except for pneumonia in 1926, and had entered the menopause at the age of 49. In the latter part of June, 1929, she felt a heavy lump in the upper outer quadrant of the right breast. This tumor gradually increased in size, causing pain, and on August 19, the overlying skin was red and inflamed. The patient was an elderly obese woman weighing 170 pounds (77.1 Kg.). Her lungs and heart were normal. Both breasts were large and pendulous. In the upper outer quadrant of the right breast was a large mass measuring 7 by 6.5 cm. The skin over the tumor, which was adherent and protruded in a moundlike eminence 2 cm. in diameter, was red, tender, inflamed and about to ulcerate. Several lymph nodes were palpable in the right axilla. A roentgenogram of the chest was negative for pulmonary metastases. The clinical diagnosis was primary operable carcinoma of the right breast with axillary metastases.

Treatment was given entirely by the radium element pack at 6 cm. distance. From September 29 until November 7, 16,000 milligram hours of treatment were given to the right axilla and an equal amount to the right supraclavicular space; 24,000 milligram hours were given to the right breast directed toward the tumor. The isodosis curve for the radium element pack at 6 cm. focal distance was such that we have computed the tissue dosage in the depth of the tumor as only 40 per cent of an erythema dose. The superficial portion of the tumor mass received one and one-half erythema doses. On December 2, the tumor and axillary nodes could no longer be palpated.

Comment.—An unusual instance is recorded of the complete clinical disappearance of a bulky mammary carcinoma, following one cycle of treatment with the radium element pack. The degree of radiosensitivity was comparable to that of many lymphosarcomas. Another unusual feature was the presence of a rapidly growing, highly radiosensitive mammary cancer in a woman of 66 years. Most mammary cancers in older women are slow growing and radioresistant. In estimating the tissue dose of any particular tumor, we consider the smallest amount of radiation which is delivered to any part of the tumor, in this instance 40 per cent of an erythema unit. This result is an excellent example of the so-called "selective cytolethal action" of the gamma rays of radium. What should be the future management of such a patient who is clinically free from disease? Experience taught us that the previously mentioned treatment was insufficient to prevent a recurrence. With only external irradiation to rely on, the interval of time between treatments would be long enough to permit any surviving cancer cells to acquire radioresistance, and the amount of irradiation would be definitely limited by the tolerance of the skin over the tumor. Since this tumor was probably highly malignant, as judged by its radiosensitivity, a radical mastectomy without preoperative irradiation would probably be accompanied by the hazard of widespread dissemination of cancer cells.

Subsequent Irradiation.—In agreement with our previous statements, we believed the safe amount of radiation to employ to be that which is capable of destroying the most radioresistant cancer; therefore on Jan. 17, 1930, 86 millicuries of radon in 30 gold seeds and 30 millicuries in 11 gold seeds were implanted in the breast and axilla, respectively. This afforded a dosage of 12 skin erythema units to the

mammary tumor; the calculation was based on the original measurement of the tumor, and the gold seeds were inserted in the breast at the site which the tumor occupied. On February 7, only three weeks following interstitial irradiation, a right radical mastectomy was performed. Residual carcinoma of the breast was found on microscopic examination; the carcinoma was so necrotic and affected by radiation that its type could not be determined. There were areas of hyaline tissue with true bone formation in the tumor; hydropic degenerated tumor cells were found in the interstices of the diseased tissue. These observations were considered indicative of metaplasia occurring in regressing cancer.

Final Comment.—The presence of cancer in the amputated breast following heavy interstitial irradiation (1,200 per cent S. E. D.) and the clinical disappearance of such a cancer following external irradiation only (40 per cent S. E. D.) indicate the wide range in radiosensitivity of the cells comprising this tumor.

Fig. 7.—(*A*) Carcinoma of the axillary segment of the right breast. Measurement of neoplasm, 7 by 6.5 cm. (*B*) Complete clinical disappearance of the cancer following treatment by the radium element pack. (*C*) Hyaline tissue, true bone formation (metaplasia) and remnants of hydropic tumor in regressing mammary cancer.

Another principle is illustrated here, namely, the employment of a dose of interstitial irradiation based on the original measurement of the large tumor which had completely disappeared following external irradiation. This principle should be applied cautiously for fear of radium necrosis. The patient is at present clinically free from disease, and the wound is well healed. Primary wound healing did not occur after mastectomy, owing to the short interval between the interstitial radiation and operation (three weeks). (See fig. 7.)

The tissue dose delivered to the tumor should always be measured and expressed in skin erythema units. This dose should be prescribed. The tables prepared in the physical department enable the clinician to

translate into terms of skin erythema units the tissue dose delivered either by external or interstitial irradiation.

Method of Measuring a Mammary Tumor.—With the patient in the recumbent posture, the transverse and vertical contours of the involved breast at the level of the tumor are taken by the adjustment of flexible lead tapes, later tracings being made on paper for permanent record. The tumor of the breast is measured in its three dimensions by calipers calibrated in centimeters. The exact location and size of the tumor are recorded on the traced contour of the breast, care being taken to show the exact depth below the level of the skin. This graphic record is used for estimating the amount of radiation delivered from external sources to the most remote portion of the tumor.

CASE 2.—*To illustrate the control of mammary cancer by the use of external and interstitial irradiation.*

O. R., an English woman, aged 57, married, applied to the Memorial Hospital in May, 1920, complaining of the presence of two small lumps in her right breast. In 1893, she had had one child whom she had nursed for five months; she had had no lactational difficulties. In March, 1920, a hysterectomy was done for fibromyoma. For two years, she had been aware of two small lumps in the right breast. This breast had undergone gradual atrophy, and the tumors were slightly painful. In the upper inner quadrant of the right breast was a small horseshoe-shaped mass, measuring 5 by 3 cm. It was definitely adherent to the superjacent skin. There were no palpable axillary or supraclavicular lymph nodes. A roentgenogram of the chest was negative for pulmonary metastasis. The clinical diagnosis was primary operable carcinoma of the breast.

Immediate treatment was instituted, a low voltage roentgen cycle to the right breast and drainage areas being employed from May 29 to June 9. On August 13, a biopsy was performed on the residual tumor of the right breast. Microscopic study of this specimen by Dr. Ewing revealed carcinoma simplex. Three additional low voltage roentgen cycles were given to the right breast and drainage areas in September and November, 1920 and in March, 1921, respectively. Dr. Frank E. Adair then gave interstitial irradiation in glass radon seeds. On Feb. 14, 1931, the patient was without clinical evidence of cancer. She has remained in excellent health for twelve years from the known date of onset, and ten and one half years from the first treatment given at the Memorial Hospital. The administration of four cycles of roentgen treatments in the course of ten months caused marked telangiectasia and sclerosis of the skin of the breast.

Comment.—The prolonged survival of this patient without clinical evidence of cancer does not indicate that a cure has been obtained. We believe that we have been successful in the production of abortive fibrosis to such a degree that the residual mammary cancer is perhaps permanently entombed in scar tissue within the breast. The depth of the dose of irradiation delivered by these roentgen treatments is insufficient to destroy the average radioresistant mammary cancer, but it can induce marked fibrosis of a cancer bed; for practical purposes this result might be considered as equivalent to a cure. (See fig. 8.)

We shall give a summary of the steps in the calculation of the tissue dose when treatment has already been given.

A. External Radiation

1. Calculate the percentage erythema dose on the skin for each treatment.
2. Determine the distance from the depth of the tumor mass to the center of each portal on the skin.

3. From the proper curve for the depth dosage determine the percentage of surface radiation delivered at the given depth for each treatment.
4. Multiply this percentage for each treatment by the percentage given in 1. This gives the tissue dose for each treatment.
5. Add results given by 4 for all external treatments.

Fig. 8.—(*A*) Carcinoma of the upper central segment of the right breast. (*B*) Telangiectatic mammary skin eight years following low voltage irradiation. (*C*) Photomicrograph of the specimen taken for the original biopsy; carcinoma simplex.

B. Interstitial Radiation

1. Determine the three dimensions of the tumor mass.
2. Decide what sphere or group of spheres define it.
3. (*a*) For a single sphere the diameter of which is the largest dimension of the mass, by means of the figures in the column for this diameter in the table for gold seed doses, determine the tissue doses by the number of millicuries used.

(*b*) For a group of spheres, divide the total number of millicuries by the number of spheres; then in one sphere, determine the dose as in *a*. This is the tissue dose from interstitial radiation.

C. Add the results of *A* 5 and *B* 3 for the total tissue dose. This is the minimum dose delivered in the tumor mass.

We shall now give a summary of the steps in the calculation of the radiation necessary to give a specified tissue dose.

1. Specify the tissue dose to be given (the minimum).
2. Decide what external treatment is advisable.
3. Determine the distance from the depth of the lesion to each portal in the skin for external radiation.
4. Calculate the tissue dose from this external radiation as in the case for treatment already given. (See the preceding outline, sections *A* 3 and 4).
5. Subtract the tissue dose thus obtained from the specified dose. The remainder is to be given by interstitial radiation.
6. Determine the three dimensions of the lesion.
7. Decide what sphere or group of spheres to consider as defining it.
8. (*a*) For a single sphere the diameter of which is the largest diameter of the mass, determine the number of millicuries necessary to give the dose specified in 5. This diameter will be found in the table for gold seed doses.

(*b*) For a group of spheres, determine the number of millicuries necessary to give the dose specified in 5 from data found in the column for the diameter of one sphere of the group. Multiply this by the number of spheres. This gives the dose of interstitial irradiation required.

The mammary gland will tolerate safely an enormous dose of interstitial irradiation. The first time 40 millicuries were introduced into the breast, we were somewhat fearful of the consequences. As no untoward effects were evident, the number of millicuries was cautiously increased until as much as 133 millicuries were given in gold seeds. The degree of radium reaction in the breast is proportionate to the amount of interstitial irradiation, but even a large amount is insufficient to injure seriously the skin of the breast. Small breasts are given less interstitial treatment. One should bear in mind that radon implanted in a breast irradiates in all directions. In the estimation of the required dosage, care should be exercised to avoid a possible permanent injury to the wall of the chest or underlying pleura by overdosage, especially when the tumor is contiguous to the ribs. We have not observed pleuritis as a complicating sequel to these treatments.

CASE 3.—*To illustrate the great tolerance of the mammary gland for interstitial irradiation.*

M. P., a white woman, aged 48, married, applied to the Memorial Hospital on Feb. 25, 1930, complaining of a lump in the left breast. She had had one miscarriage but no other pregnancies. In 1930, she had had a hysterectomy for pelvic inflammatory disease. Fifteen months prior to admission, she fractured her left wrist and traumatized her left breast by a fall. In November, 1929, she first noticed a tumor in the upper inner quadrant of the left breast. Since then there

had not been any change in the size of this tumor, mastalgia, secretion from the nipple, loss of weight or cough. On physical examination, a tumor 6.5 by 5 by 3 cm. was found to occupy the upper inner quadrant of the left breast. Both breasts were large and pendulous. The skin over the tumor was definitely adherent. There were no palpable lymph nodes in the axilla or supraclavicular spaces. A roentgenogram of the chest was negative for pulmonary metastases. The clinical diagnosis was primary operable carcinoma of the left breast.

On Feb. 27, 1930, 133 millicuries of radon in 40 gold seeds were inserted into the tumor, constituting a tissue dose of 2,070 per cent S. E. D. External irradiation was not given. The tumor disappeared in two months after treatment, but the excoriation of the skin was slow in healing. On June 26, three and one half months after irradiation, a left radical mastectomy was performed. On section of the breast, the tumor had diminished markedly in size; it measured 2 by 1.5 by 1.5 cm., and was completely necrotic. The axillary lymph nodes were not involved. Microscopic examination showed the tumor to be a carcinoma simplex that had undergone complete radium necrosis. The wound healed well with the exception of slight necrosis along the line of incision. On Jan. 26, 1931, there was no clinical evidence of cancer; the wound had healed well without inflammation or necrosis.

Comment.—This patient accidentally received twice the dose considered necessary to sterilize the cancer. The large size of the breasts and the abundance of enveloping fatty tissue account in large part for the tolerance of this breast to such an enormous dose of irradiation. Of equal interest is the fact that the healing of the wound after wide radical mastectomy was only slightly impaired.

In radiation therapy, the dose is usually dependent on the relative susceptibility of the cancer and the normal environmental tissues, e. g., the therapeutic index equals $\frac{\text{susceptibility of normal tissue}}{\text{susceptibility of tumor}}$. Fortunately, we have seen that the breast will safely tolerate sufficient interstitial irradiation to destroy the most radioresistant mammary cancer. On the basis of our histologic studies of amputated breasts as treated, we now believe that the tissue dosage necessary to effect destruction of a radioresistant mammary cancer, approximates twelve erythema doses. It is true that sufficient time has not elapsed to estimate the sterilizing dose for mammary cancers treated by irradiation without subsequent mastectomies. Although mammary cancers vary considerably in radiosensitivity, we believe that the safest procedure is to treat all with the same sufficient dose, because radiosensitivity cannot always be determined before operation, and the same tumor may contain radioresistant and radiosensitive portions.

As can be seen in table 5, many of the carcinomas received supralethal doses. When the tumor mass is small an overdose of interstitial irradiation may safely be given; this is usually done intentionally. If the tumor is 3 cm. in diameter, the dosage may be planned for a mass 5 cm. in diameter, thereby irradiating heavily the all-important, growing edge of the cancer.

Whenever the carcinoma has been destroyed with complete regression of the palpable mass and satisfactory repair, we assume that the dose has been optimum. If radionecrosis and destruction and ulceration of the skin follow (of which we have observed only one instance), we consider the dose as excessive. If the cancer almost disappears but later resumes its growth activity, we know that the dose has been inadequate. If there has been no measurable diminution in the size of a mammary cancer that received the maximum tissue dose from preliminary external irradiation, we are dealing with a radioresistant carcinoma. If the carcinoma diminishes markedly in size and remains indefinitely as a firm,

TABLE 6.—*Efficient Doses of Irradiation for Primary Carcinomas of the Breast*

Skin Erythema Doses	Sublethal Doses	Lethal or Supralethal Doses
1	6	..
From 1 to 2	9	2*
From 2 to 3	1	..
From 3 to 4	..	..
From 4 to 5	..	..
From 5 to 6	..	..
From 6 to 7	2	..
From 7 to 8	2	..
From 8 to 9	1	2
From 9 to 10	3	3
From 10 to 11	1	2
From 11 to 12	..	4
From 12 to 13	..	4
From 13 to 14	1†	2
From 14 to 15	1‡	..
From 15 to 16	..	1
From 16 to 17	..	1
From 17 to 18	..	1
From 18 to 19	..	1
From 19 to 20	..	3
20+	..	2

* In two radiosensitive carcinomas, mastectomies were not performed. Clinical evidence of cancer was not present after one and two years, respectively.
† Improperly placed gold seeds.
‡ The breast was amputated less than four weeks after the insertion of gold radon seeds.

inactive mass, we realize that we have attained abortive fibrosis and restraint of the growth of the tumor, which is the object of an inhibitory dose.

CASE 4.—*To illustrate the present method of treating patients for mammary cancer by external and interstitial irradiation followed by radical mastectomy.*

E. P., a white woman, aged 46, married, applied to the Memorial Hospital on May 10, 1929, complaining of a large lump in the left breast. She had three children, aged 23, 21 and 18 years. Following the birth of the first child, her left breast became caked. When this subsided, a residual lump remained which had begun to increase in size during the past few months before admission. In the upper outer quadrant of the left breast was a bulky, firm tumor measuring 5.5 by 3 by 3 cm. The tumor was firmly adherent to the overlying skin. There were many large palpable lymph nodes in the left axilla. The clinical diagnosis was primary operable carcinoma of the left breast with axillary metastases.

Immediate treatment was instituted by giving 16,000 milligram hours by the radium element pack at 6 cm. distance over the left breast (May 29, 1929). On

July 10, this was followed by the implantation of 18 gold seeds totaling 41.15 millicuries, in the tumor of the left breast, and the insertion of 3 platinum filtered needles totaling 159 millicuries for a dosage of 700 millicurie hours in the left axilla. Five and one half weeks later, on August 20, a left radical mastectomy was done. The wound healed by primary intention. The tumor received slightly more than 9 skin erythema doses of irradiation. On microscopic examination, a very cellular carcinoma was recognized, but it was too necrotic to classify or grade. No viable carcinoma was seen anywhere. There was some squamous metaplasia of the ducts. At the last examination, on Feb. 18, 1931, there was no evidence of recurrence.

Comment.—The tissue dose of 940 per cent S. E. D. delivered by combined external and interstitial irradiation was sufficient to destroy completely a cellular carcinoma of the left breast. (See fig. 9.)

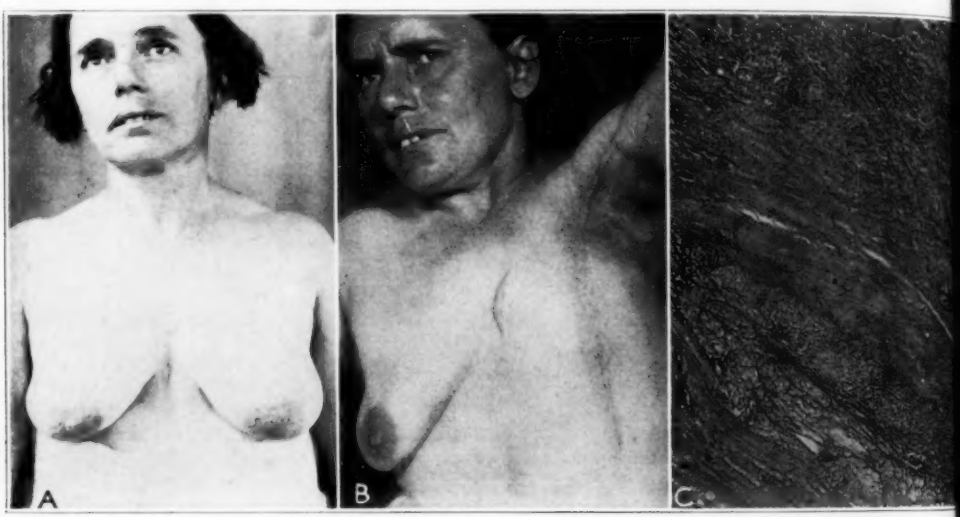

Fig. 9.—(*A*) Carcinoma of the upper outer quadrant of the left breast. (*B*) Postoperative view of patient showing integrity of skin and character of wound healing. (*C*) Complete necrosis of a very cellular mammary carcinoma (table 9, case 8).

CASE 5.—*To illustrate the present method of treating patients for mammary cancer by external and interstitial irradiation followed by radical mastectomy.*

M. Z., a Russian woman, aged 38, married, applied to the Memorial Hospital on Sept. 4, 1929, complaining of pain in her right breast and the presence of a lump in her right armpit. She had been pregnant only once, for which a cesarean section had been performed; the child was stillborn. She detected the lump in her right axilla only three days before application to the Memorial Hospital. In the central portion of the right breast posterior to the nipple was an irregular tumor measuring 6 by 6 by 4 cm. The nipple was retracted and fixed. The skin of the areola was adherent to the tumor. A node 2 cm. in diameter was situated in the lower part of the right axilla. A roentgenogram of the chest was negative. The diagnosis was operable carcinoma of the right breast with axillary metastasis.

Preliminary treatment was instituted by giving a high voltage roentgen cycle to the right breast and drainage areas (from September 4 to 16). This was followed on September 21 by the implantation of 49.38 millicuries of radon in 14 gold seeds into the tumor of the right breast. Four weeks later, on October 18, a right radical mastectomy was performed. The wound healed by primary intention. In the sectioned breast, the tumor was surrounded by a hemorrhagic, necrotic zone of tissue. Histologically, there was marked productive fibrosis, profound metaplasia of the ducts, and marked, practically complete, necrosis, of the tumor, which was an infiltrating duct carcinoma. The metastatic carcinoma in the axilla and lymph node was also largely destroyed. At the time this article was written, sixteen months later, there was no evidence of recurrence.

Comment.—A tissue dose of 1,020 per cent S. E. D. delivered by combined external and interstitial irradiation was sufficient to produce marked necrosis and productive fibrosis in an infiltrating carcinoma of the breast. (See fig. 10.)

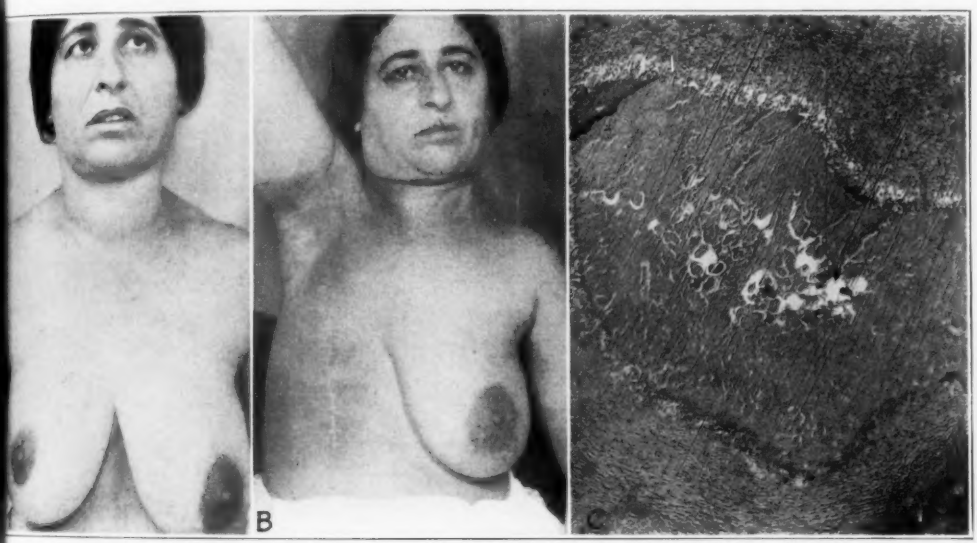

Fig. 10.—(*A*) Carcinoma of the central part of the right breast. (*B*) Postoperative view of patient showing integrity of skin, character of the wound healing and maintenance of good function in the arm. (*C*) Photomicrograph showing marked necrosis of duct carcinoma (table 10, case 5).

IRRADIATION OF THE AXILLA

The axilla is irradiated whether or not axillary nodes are palpable, for we have shown that there is a possibility of error of 17 per cent in determining the presence or absence of involved axillary nodes. The axillary is irradiated by preoperative roentgen rays or radium element pack followed by interstitial gold-filtered radon distributed along the gland-bearing areas. In general, we have found the management of axillary nodes one of the big problems in the treatment for mammary cancer by radiation, and we believe that our present means of attack is not wholly satisfactory.

The axillary nodes are variable in their distribution and cannot be accurately localized at fixed anatomic points. Ewing has said, "Unlike cervical lymph nodes, axillary nodes may lack complete capsules and are readily traversed by tumor cells." The dispersion of active carcinoma cells in the axillary fat seriously hinders the cure of cancer in this location, for these cells divide rapidly in spite of heavy external irradiation. As long as the cancer cells remain within the node, external irradiation has a perceptible influence because of the pressure atrophy, vascular occlusion with ischemia, and strangulation. The difficulties attendant on estimation of depth dosage from external radiation are several. The axilla is a truncated cone or rather an equilateral four-sided pyramid, which varies in shape and depth in different persons. A certain amount of radiation reaches the axillary contents from the treatments given over the corresponding supraclavicular space. When multiple metastases to several axillary nodes have occurred, the correct estimation of the tissue dosage for these nodes is impossible. When one or two, quite large, movable nodes are present, the tissue dose can be calculated and delivered with considerable ease.

External irradiation alone is inadequate in the treatment for carcinomatous metastases to the axilla, as it is in that for carcinoma of the breast. Interstitial irradiation must be employed if metastases are present. The introduction of gold radon seeds into small axillary nodes has turned out to be a difficult matter, for without opening the axilla, one cannot accurately localize the nodes at the time of introduction, and satisfactory implantation may be impossible. On opening the axilla in the endeavor to isolate nodes, we frequently find that it is easier to dissect out fat and nodes than to attempt to introduce radium into separate nodes. Whenever the nodes are large, the radon can be introduced easily into their substance without surgical exposure (table 13, patient E. H.). The gold seeds are implanted in the axilla at the same time and with the same technic as they are in the breast. Rows of gold seeds are placed along the lymphatic trunks leading to the axilla and along the important intermuscular trunks. Stronger gold seeds are deposited in the region of the pectoral group of nodes along the inferior posterior aspect of the pectoral muscles, adjacent to the anterior insertion of the latissimus dorsi, and in the region of the subclavicular group, a most important region, as these nodes are the immediate relay stations prior to involvement of the supraclavicular nodes. The former nodes are reached by transfixion of the axillary skin, whereas the needles are inserted into the latter region by a row of transcutaneous punctures below and parallel to the outer half of the clavicle. While the needle points are guided into the apex of the axilla by careful palpation, the left hand pushes the axillary vessels high out of harm's way. The gold radon seeds should

never be placed nearer than 1 cm. to the branches of the brachial plexus, otherwise intractable neuritis may ensue. No edema of the arm has ever followed these treatments. The axillary fat becomes drier than normal, and there is some fibrosis, but these changes do not handicap subsequent axillary dissection.

CASE 6.—*To illustrate the necessity of interstitial irradiation of carcinomatous metastases to the axillary lymph nodes.*

S. Z., a Polish woman, aged 34, married, applied to the Memorial Hospital on Dec. 29, 1928, complaining of a lump in her left arm pit. Menstruation had always been normal. She had four children, aged from 5 to 14 years, whom she

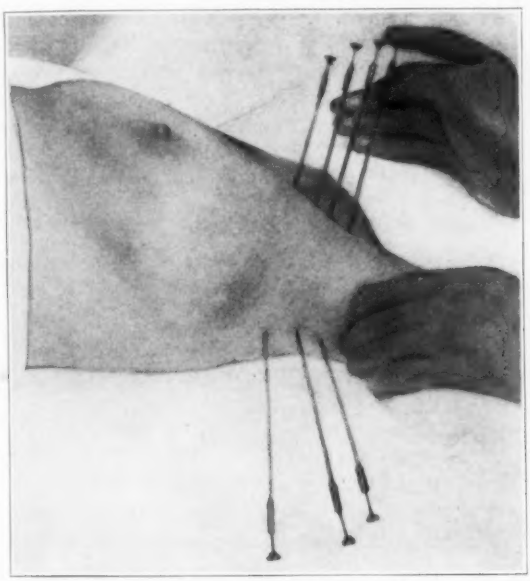

Fig. 11.—Technic of implantation of gold radon seeds in the left axilla.

had nursed for from fourteen to eighteen months without lactational difficulties. On Oct. 1, 1928, she accidentally felt a lump, the size of a hen's egg, in her left axilla. There had never been any mastalgia, discharge from the nipple, loss of weight, dyspnea or cough. On physical examination, there was chloasma and slight hypertrophy of the thyroid gland. The external and internal genitalia were apparently normal. The right breast was clinically free from disease. In the lower outer quadrant of the left breast were two, small, barely palpable nodules, about the size of a hazelnut. In the left axilla were five or six large, discrete, hard lymph nodes, measuring 5 cm. in diameter. A small lymph node in the left supraclavicular space was thought to contain metastatic carcinoma. The clinical diagnosis was inoperable carcinoma with metastases to the axillary and supraclavicular lymph nodes.

Immediate treatment was instituted, employing a high voltage roentgen cycle to the left breast and drainage areas (from December 31 to Jan. 7, 1929). This was followed by radium element pack treatments, 14,000 milligram hours at a

distance of 6 cm., to the left axilla and left supraclavicular space (from January 19 to January 27). By August, the supraclavicular node was no longer palpable; the axillary nodes were still very large and hard, and the nodules in the breast were unchanged. At this time, 21.3 millicuries of radon in 10 gold seeds were implanted in the left axilla; the tiny nodules in the breast likewise received interstitial irradiation (ten skin erythema doses). By October, the mammary and axillary tumors had disappeared; there had been no recurrence to Feb. 12, 1931. She experienced amenorrhea from November, 1929, to February, 1930, at which time a large left ovarian tumor was recognized as complicating pregnancy. At laparotomy, a panhysterectomy was performed. The left ovary was 15 by 10 cm. in diameter; the microscopic diagnosis was metastatic tubular carcinoma of the type in the breast. The patient had had no clinical evidence of cancer to Feb. 12, 1931.

Comment.—The bulk of the axillary metastases and the small size of the primary cancer in the breast led us to believe that the neoplasm was anaplastic. This carcinoma was sufficiently radioresistant to be refractory to external irradiation. We expect the late appearance of other metastases, although a year has elapsed since the last metastasis (ovarian) was treated. External irradiation obviously could not deliver a lethal dose into the substance of the axillary tumor, which was apparently accomplished by the implantation of gold radon seeds.

Unfiltered Interstitial Irradiation.—In the early part of the last decade, radon was collected in tiny glass capillary tubes, which were subdivided into shorter segments called "bare glass radon seeds." For the treatment for carcinoma of the breast, these glass-filtered radon implants were inserted interstitially to deliver a dosage of approximately 1 millicurie for each cubic centimeter of tumor tissue. The general tendency was to give repeated treatments in small doses. The glass wall of the capsule filtered out the alpha rays and some of the soft beta rays, but sufficient of the latter escaped to exert a caustic action on the tissue surrounding the seeds. Enveloping each glass seed was a sphere of coagulation necrosis which in turn was surrounded by an outer zone of nonviable but recognizable carcinoma. The beta rays were stopped by the carcinoma, but the more penetrating gamma rays extended farther peripherally to sterilize a still larger sphere of tissue. These "bare glass seeds" produced much more necrosis than occurs from gold-filtered implants. The sequence of events in the irradiated breast was carbonization, colliquation and dense fibrosis. Dr. Ewing, who studied these histologic changes with the microscope, has long maintained that the glass-filtered radon seeds are superior to gold seeds for interstitial irradiation of the breast.

Radium Puncture by Platinum-Filtered Needles.—In 1920, we first employed hollow, radon-containing needles for interstitial irradiation of mammary cancer. Each needle had a steel shank from 8 to 10 cm. long, to which was attached a platinum point 4 cm. long, with a wall 0.4 mm. thick. Into the platinum tip from 60 to 80 millicuries of radium emana-

tion were introduced and sealed with paraffin. The needles were sterilized by immersion in alcohol. The longitudinal and transverse diameters of the tumor having been determined by caliper measurement and the average thickness estimated, the cubic contents were calculated. At first, the dosage used was 25 millicurie hours per cubic centimeter; later the dosage was increased to 50 millicurie hours per cubic centimeter of tissue. Under procaine hydrochloride anesthesia, we passed the needles through the skin and into the tumor along two peripheral transverse lines, endeavoring to place them equidistant from the anterior and posterior surfaces. Now that we have available more accurate data concerning cancericidal doses of radium, we can appreciate in retrospect the remarkably good results obtained with these radon needles in consideration of the dose delivered. One serious objection to their usage was the attendant trauma. The needles were also directed subpectorally toward the axillary apex and downward into the axilla from the infraclavicular region.

Another device for this method of treatment is the employment of hypodermic needles of lengths suited to the size of the tumor; the lumina of these needles are threaded with gold radon seeds in tandem formation, and the ends of the needles are plugged with soft wax. These needles may be used to perforate the tumor in various directions.

CASE 7.—*To illustrate the interstitial use of platinum-filtered radon needles.*

S. S., a Russian woman, aged 41, married, applied to the Memorial Hospital on June 20, 1925, complaining of a lump in the upper outer quadrant of the right breast. In 1907, she gave birth to a child whom she did not nurse. The lump in the breast had been present for eighteen months and had gradually increased in size. On physical examination, the tumor measured 6 by 3 by 3 cm., was ovoid in shape and adherent to the superjacent skin. There were small palpable nodes in the axillae, which were not considered neoplastic. A roentgenogram of the chest was negative for pulmonary metastasis. The diagnosis was primary operable carcinoma of the right breast.

In June, 1925, four platinum-filtered needles, containing a total of 92 millicuries, were inserted through the tumor of the breast for six and a half hours. This was preceded by a low voltage roentgen cycle of irradiation to the right breast and drainage areas. In July, a right radical mastectomy was performed. Five centimeters from the nipple was an indurated area 2 cm. in width, in which small necrotic foci were evident. There was considerable chronic inflammation in the fatty tissue and some liquefaction necrosis. There was no macroscopic evidence of cancer; microscopically, however, a small cell, anaplastic, infiltrating carcinoma was found to be markedly injured by the irradiation and enclosed in scar tissue. Amputation of the breast was followed by two postoperative low voltage roentgen cycles in the following October and in August, 1926. At the last examination, on Jan. 19, 1931, there was no evidence of cancer. There was some lymphedema of the right arm and hand.

Comment.—Considering the very small dose of radiation delivered into this tumor, the histologic effect on the cancer and the subsequent freedom from disease are quite satisfactory. The pathologic findings indicated the possibility of complete destruction of mammary cancer by heavier interstitial irradiation.

CASE 8.—*To illustrate the treatment for primary operable mammary cancer by external irradiation supplemented by interstitial radiation in the form of platinum-filtered radon needles.*

R. O., a Norwegian woman, aged 43, married, applied to the Memorial Hospital on Nov. 14, 1924, complaining of a lump in the right breast. She had had one child in 1916 whom she had nursed without lactational difficulties. Two days prior to admission, she accidentally discovered a painless lump in her breast. This lump involved the upper outer segment, and was adherent to the superjacent skin. There were no palpable lymph nodes in the axilla or supraclavicular space. A roentgenogram of the chest was negative for pulmonary metastases. The diagnosis was primary operable carcinoma of the breast.

In December, two platinum-filtered radon needles were inserted in the right breast for a dosage of 480 millicurie hours. This treatment was preceded by a

Fig. 12 (case 8).—Appearance on March 10, 1930, of carcinoma of the right breast treated in 1924 by interstitial platinum-filtered radon needles.

low voltage roentgen cycle to the right breast and drainage areas. In March, 1925, two platinum-filtered radon needles were inserted into the tumor of the breast for a dosage of 420 millicurie hours. This treatment was followed by another low voltage roentgen cycle to the right breast. In March, 1926, a radon tray, at a distance of 3 cm., was applied over the mammary tumor for a dosage of 3,000 millicurie hours. In the following June, an additional low voltage roentgen cycle was given to the right breast. In September, seven platinum-filtered radon needles were inserted into the right breast for a dosage of 1,160 millicurie hours. During this time the lump in the breast regressed gradually in size; a small fibrosed nodule remained which was considered to be either scar tissue or residual tumor. In 1927, the right axilla received 30,000 millicurie hours at a distance of 6 cm. with 2 mm. of brass filter, by a radon emanation pack of 70 sq. cm. surface-radiating area. The patient has remained in excellent health without clinical evidence of carcinoma. (See fig. 12.)

Comment.—External irradiation together with interstitial irradiation by means of radon needles can suffice to treat mammary cancer which is confined to the breast. The proper dosage for this method of treatment is difficult to estimate and therefore somewhat empiric.

A CRITIQUE OF KEYNES' METHOD OF IRRADIATING CARCINOMA OF THE BREAST

More recently Keynes has placed needles of variable length and of variable content of radium element in the breast proper, the axilla, beneath the pectoralis major muscle, above the clavicle, below the clavicle and over the first three or four intercostal spaces. These needles are left in place for five days. Allowing for the relatively recent period in which this work was done, Keynes has secured encouraging results with his technic. By April, 1929, he had subjected ninety patients to this procedure. In the first fifty cases, biopsy was done at the time the needles were removed. Since this time he has relied on the accuracy of his clinical diagnosis for statistical data. On several occasions, a nodule of carcinoma developed in the scars of the biopsy even though irradiation was in progress. We commend the principles underlying this technic of interstitial irradiation, but find certain objections to the assumptions made concerning its effectiveness. The computation of correct tissue dosage by this method is very difficult because the distribution of the radon in the needles does not constitute point sources for calculation. In only a few cases did Keynes excise the irradiated tumor; the remaining breasts were left intact, so that now no one knows whether the carcinomas were destroyed completely or are viable and latent in the deep scars within the breasts (abortive fibrosis). In his three available papers, he cited the same two cases wherein postradiation excision was performed; the dosage was said to be inadequate because carcinoma was found in each specimen, although one of these patients has remained clinically free from cancer for over five years. Our own experience has taught us not to rely on the clinical disappearance of the carcinoma thereby leaving the breast in situ, but (until a safe dose is determined) to amputate these irradiated breasts and to ascertain the dosage that affords microscopic evidence of complete destruction of the cancers. The results by any other method must be attained by trial and error.

THE INFLUENCE OF PREOPERATIVE IRRADIATION ON WOUND HEALING

The influential factors in wound healing following radical mastectomies for carcinomas of the breast that have been treated preoperatively by irradiation are several: (*a*) The presence of an open, infected lesion as a source of wound contamination; this same hazard obtains in non-irradiated cases, but is of more serious import here because of the tenacity with which infection persists in irradiated tissues. (*b*) The adiposity of the breast and the axilla influence healing; wound healing in obese patients is difficult in the best circumstances, but in irradiated fatty tissue the process is even slower. (*c*) The size of the tumor, especially in comparison with the size of the breast. (*d*) The amount

of skin sacrificed and the consequent degree of tension; with the progress of time, the vascularity of irradiated skin gradually diminishes, a condition that impedes wound healing. (*e*) The employment of external irradiation; all other conditions being equal, the tissue dosage delivered by external irradiation through the skin to the tumor, provokes far greater injury to the skin than an equivalent dosage given interstitially. (*f*) The use of interstitial irradiation and the total quantity of radium emanation employed. The dosage of interstitial irradiation should be limited by the size of the breast. This problem has been readily solved and is dependent somewhat on the relation of the size of the tumor to that of the breast that contains it. When a bulky carcinoma occupies almost the entire breast, a lethal dose of interstitial irradiation may destroy the skin, produce ulceration, delay amputation and impair the healing of the wound. (*g*) The proximity of the gold radon seeds to the wall of the chest. If the carcinoma is situated deeply in the breast, in contact with the thoracic wall, care must be exercised in the dosage and placement of the gold radon seeds, otherwise late radiation effects even pleural, periosteal or perichondrial damage, and tardy bone necrosis may ensue. (*h*) The time interval between the completion of the irradiation and the operation. This is evidently the most important factor. The allowance of an optimal interval diminishes the risk of infection, permits the subsidence of the inflammatory reaction in the skin of the breast, affords the necessary time for destruction of the tumor by irradiation, gives the deeper substance of the breast and contiguous tissues an opportunity to recover from the intense reaction to the radium, and thus insures uncomplicated wound healing. From six to ten weeks should elapse following interstitial irradiation before radical amputation. When the operation is done sooner, additional hemostasis is necessary because of the post-radiation hyperemia present, and the fresh wound shares in the tissue destruction. When the operation is performed some months after massive overirradiation, the consequent fibrosis and ischemia frequently hinder the process of repair in the wound.

In an analysis of the cases of delayed or secondary wound healing, we have perceived that the interval of time between heavy irradiation and operation was short, with one exception, in which the dosage was too large for the size of the breast.

Case 1, table 11, 635 per cent S. E. D. Interval of 29 days.
Case 2, table 11, 650 per cent S. E. D. Interval of 36 days.
Case 2, table 9, 1,000 per cent S. E. D. Interval of 20 days.
Case 8, table 13, 1,000 per cent S. E. D. Interval of 27 days.
Case 9, table 11, 1,200 per cent S. E. D. Interval of 21 days.
Case 6, table 9, 1,500 per cent S. E. D. Interval of 36 days.
Case 17, table 13, 2,150 per cent S. E. D. Interval of 44 days.

Patient	Age	Location of Tumor, Size	Rate of Growth	Axilla*	Clinical Index of Malignancy	Operation	Healing of Wound	Roentgen Treatments	Tissue Dosage in Breast, Per Cent, Skin Erythema Doses	Interval Between Irradiation and Operation	End-Result	Gross Pathologic Anatomy	Pathologic Histology
L. W.	51	Left, 3.75×2.5 cm.	Rapid	Adenopathy	B	2/10/28, radical mastectomy	Slough	1/13/28, 2 low voltage treatments	100	4 wk.	Metastases to the lungs	Tumor, 1×1 cm.	Carcinoma simplex; fibrosis; slight atrophy of tumor cells; invasion of lymphatics; mucinous changes in stroma
L. R.	46	Left, 9×6 cm.	Rapid	Adenopathy	B+	None	.....	1/10/28, 2 low voltage treatments	100	....	2/26/28, died		
B. M.	71	Left, 4.75×3.5 cm.	Slow	0	A	12/16/27, local mastectomy	Primary healing	11/18/27, low voltage heavy treatments	110	4 wk.	8/15/29, died from cardiac failure; no cancer	.....	Carcinoma simplex, grade 2 radioresistant; abortive fibrosis as result of local vascular change; bulk of tumor relatively unaltered
T. S.	42	Right, 4.25×2.5 cm.	Slow	Adenopathy	B	6/29/28, radical mastectomy	Good healing	5/29/28, 2 high voltage treatments	130	1 mo.	No evidence	Tumor, 1.5×1 cm.	Adenocarcinomatous foci in fibro-adenoma; axillary node carcinomatous
Y. N.†	72	Left, 3.5×2.25 cm.	Slow	Adenopathy	B—	.....	.....	5/22/28, 2 high voltage treatments	130	....	No evidence	Evidently very radiosensitive	
L. F.	35	Right, 3.5×2.5× 2.5 cm.	Rapid	Adenopathy	C	6/28/28, radical mastectomy	Primary healing	5/23/28, 2 high voltage treatments	135	16 days	3/19/30, died; metastases to the lungs and bone	Tumor, 1.5 cm.	Infiltrating adenocarcinoma; much fibrosis; viable tumor
E. D.	46	Right, 3.5×3.5 cm.	Rapid	Adenopathy	C—	1/27/28, radical mastectomy	Good healing	1/17/28, 2 high voltage treatments	140	10 days	Metastasis to the skin, lung and skull	Tumor, 2×2 cm.	Gelatinous adenocarcinoma; slight atrophy of tumor cells; axillary node carcinomatous
R. B.	45	Right, 5.5×3 cm.	Slow	Adenopathy	B—	6/22/28, radical mastectomy	Slow healing at lower end of wound	5/29/28, 2 high voltage treatments	140	3 wk.	Cerebral metastases	Tumor, 5×5 cm.	Adenocarcinoma, grade 2 radioresistant; marked fibrous tissue reaction
K. C.	64	Right, 10×5×4 cm.	Rapid	Adenopathy	B+	7/20/28, radical mastectomy	Primary healing	5/22/28, 2 high voltage treatments	140	2 mo.	No evidence	.....	Duct carcinoma with early infiltration; viable tumor, but atrophic and sloughing; fibrosis and calcification
M. H.	42	Left, 4.25×4.25 ×2.5 cm.	Moderate	Adenopathy	B	6/28/29, radical mastectomy	Wound infected	6/5/29, 2 high voltage treatments	160	23 days	7/21/30, small recurrent lump in the left axilla	Tumor, 2×2 cm.	Infiltrating tubular adenocarcinoma; considerable hydropic degeneration; axillary nodes free from cancer
E. B.	61	Right, 4×2.5× 2 cm.	Rapid	Adenopathy	B	.....	.....	12/9/27, 3/6/28, 10/24/28, high voltage treatments	100 Cannot 100 be 70 added		2/2/29, died		

* Axillae also received roentgen treatments.
† The clinical diagnosis was carcinoma because of the adherence to the skin, the firmness, the retraction of the nipple and the axillary adenopathy.

TABLE 8.—*Patients with Primary Operable Carcinoma of the Breast Treated by Radium Element Pack*

Patient	Age	Location of Tumor, Size	Rate of Growth	Axilla*	Clinical Index of Malignancy	Operation	Healing of Wound	Radium Element Pack Treatments	Tissue Dosage in Breast, per Cent, Skin Erythema Doses	Interval Between Irradiation and Operation	End-Result	Gross Pathologic Anatomy	Pathologic Histology
M. T.	62	Left, 12×9×7 cm.	Rapid	Adenopathy	B+	10/4/29, radical mastectomy	Primary healing	8/29/29, 30,000 mg. hr. at 10 cm.	40 in 12 days	5 wk.	Metastasis to the liver	Soft hemorrhagic tumor	Infiltrating duct carcinoma; hyalinization of stroma; swelling, hydrops and atrophy of tumor cells; axillary nodes carcinomatous
M. S.	67	Right, 6×5 cm.	Moderate	0	A	10/1/29, radical mastectomy	Not good in axilla	9/6/29, 16,000 mg. hr. at 6 cm.	40 in 4 days	3 wk.	Axillary nodes	.....	Scirrhous carcinoma, radioresistant; invading fat diffuse; dense hyaline stroma
I. S.	43	Left, 4×4 cm.	Moderate	0	A+	10/11/29, radical mastectomy	Good healing	9/14/29, 16,000 mg. hr. at 6 cm.	50 in 2 days	4 wk.	No evidence	Soft nodule in breast	Intraductular and intracystic adenocarcinoma; no apparent effect caused by irradiation
M. P.	47	Right, 6.5×5.5 cm.	Moderate	Adenopathy	B	9/20/29, radical mastectomy	Slough of edges, secondary	7/24/29, 32,000 mg. hr. at 6 cm.	85 in 10 days	2 mo.	No evidence	Tumor, 3×2×2 cm.; slightly necrosed	Infiltrating duct carcinoma, grade 2 radioresistant; hyalinization of stroma; collagen swelling; necrosis of fat; atrophy and hydrops of tumor cells; acidophilic cells with giant nuclei
R. B.	64	Right, 5×5 cm.	Slow	Adenopathy	B—	1/10/30, radical mastectomy	Good healing	7/31/29, 16,000 mg. hr. 10/3/29, 16,000 mg. hr. both at 6 cm.	50†	2 mo.	No evidence	.....	Carcinoma simplex, grade 2 radioresistant; central radium necrosis due to thrombotic occlusion of vessels; peripheral tumor cells unaltered
B. M.	55	Right, 2 masses, 3×2 cm. and 2×2 cm.	Rapid	Adenopathy	C—	No operation pulmonary tuberculosis	.....	7/26/29, 32,000 mg. hr. at 6 cm.; total to two masses	100 100		No evidence, no palpable lump; radiosensitive		
A. G.	44	Left, 5×4×3 cm.	Moderate	0	A	Operation refused	.....	7/17/29, 32,000 mg. hr.; 2/16/30, 16,000 mg. hr.; both at 6 cm.	105† 65†		Complete disappearance after first treatment; radiosensitive; later reappearance		

* The axillae also received treatment by radium element pack.
† These tissue doses cannot be added because of the time interval between treatments.

TABLE 9.—*Patients with Primary Operable Carcinoma of the Breast Treated by Interstitial Irradiation*

Patient and Age	Location of Tumor, Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Interstitial, Millicuries	Irradiation, Gold Seeds	Tissue Dosage in Breast, per Cent Skin Erythema Dose	Axillary Irradiation	Interval Between Irradiation and Operation	End-Result	Gross Pathologic Anatomy	Pathologic Histology
L. F. 40	Right, 4×4× 3.5 cm.	Moderate	Adenopathy	B+	5/29/30, radical mastectomy	Primary healing	4/23/30, 29.3	12	1,000	0*	5 wk.	No evidence	Hemorrhage and necrosis in tumor, 2×2×2 cm.	Complete destruction of carcinoma in the breast; one axillary node contained cellular adenocarcinoma
B. K. 60	Left, 3×2× 2 cm.	Rapid	0	A	6/13/30, radical mastectomy	Axilla healed slowly	5/21/30, 20	8	1,000	0	3 wk.	No evidence	Necrotic tumor, 2 cm. in diameter	Infiltrating comedocarcinoma; myxomatoid degeneration; marked changes caused by irradiation; questionable viability
L. H. 56	Right, 6×5.5× 4 cm.	Moderate	Adenopathy	B	10/3/30, radical mastectomy	Primary healing	7/11/30, 64.5	23	1,200	20 mc. in 7 seeds†	12 wk.	No evidence	Hemorrhagic, necrotic tumor, 3×3×2 cm.	Complete destruction of tumor in the breast; hydropic small celled tubular carcinoma in two axillary lymph nodes
A. C. 46	Right, 3.5×3 cm.	Rapid	0	A+	11/15/29, radical mastectomy	Good healing	10/25/29, 32.3	13	1,300	18.9 mc. in 11 seeds	3 wk.	No evidence	Grayish, irregular, hemorrhagic tumor	Duct carcinoma; complete destruction of the tumor; productive fibrosis; squamous metaplasia of ducts
D. M. 50	Left, 7×6× 5 cm.	Slow	0	A	12/20/29, radical mastectomy	Primary healing	10/29/29, 94.65	36	1,350	26.25 mc. in 11 seeds	7 wk.	No evidence	Fat necrosis; hemorrhage into tumor	Practically complete radium necrosis; atrophy and hydrops of tumor cells; acute thrombosis; originally a duct carcinoma
M. I. 39	Left, 4×3.5× 3 cm.	Rapid	0	B	1/31/30, local mastectomy	Healing by second intention	12/26/29, 44.38	14	1,500	29.7 mc. in 9 seeds	1 mo.	No evidence	Grossly, no tumor present	Heavily irradiated carcinoma of the breast; almost complete destruction; one small focus of tubular carcinoma of questionable viability
G. L. 43	Left, 5×4× 4 cm.	Rapid	0	B	12/13/29, radical mastectomy	Slow healing by second intention	10/29/29, 73.64	24	1,800	30.73 mc. in 13 seeds	6 wk.	No evidence	Tumor, 2.5×2.5 cm.	Infiltrating carcinoma; advanced radium necrosis of tumor; productive fibrosis surrounding regressing nonviable tumor cells; squamous metaplasia of ducts
M. P. 48	Left, 6.5×5× 3 cm.	Rapid	0	B	6/26/30, radical mastectomy	Secondary healing	3/4/30, 133	40	2,070	0	3½ mo.	No evidence	Necrotic shrunken tumor, 2×1.5 ×1.5 cm.	Carcinoma simplex; total radium necrosis

* Insufficient irradiation.
† No axillary irradiation.

TABLE 10.—*Patient with Primary Operable Carcinoma of the*

Patient and Age	Location of Tumor; Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Roentgen Treatment	Interstitial, Millicuries	Irradiation, Gold Seeds	Tissue Dosage in Breast, per Cent, Skin Erythema Dose		
										X-Rays	Interstitial	Total
E. S. 51	Right, 3×3 cm.	Slow	Adenopathy	B—	7/12/29, radical mastectomy	Fair; two small sloughs	6/5/29, 2 high voltage treatments	6/7/29, 12-13	5	160	600	760 in 5 days
J. H. 77	Left, 8×7×3 cm.	Rapid	0	B	.....	.....	1/29/30, 2 high voltage, 1 low voltage treatments	4/16/30, 44.5 (as 2 spheres)	24	135	765	Cannot add
B. H. 68	Right, 4.25×4 cm.	Moderate	Adenopathy	B	.....	.....	7/11/29, 3 high voltage treatments	7/20/29, 25	10	180	720	900 in 16 days
E. F. 58	Left, 7×3×2 cm.	Moderate	Adenopathy	B	10/2/29, biopsy	.....	12/3/29, 3 high voltage treatments	11/2/29, 38.3 (as 2 spheres)	18	150	800	950 in 28 days
M. Z. 38	Right, 6×6×4 cm.	Rapid	Adenopathy	B+	10/18/29, radical mastectomy	Primary healing	9/16/29, 2 high voltage treatments	9/21/29, 49.4	14	120	900	1,020 in 18 days
M. B. 50	Left, 5.5×5 cm.	Rapid	Adenopathy	C—	4/25/30, radical mastectomy	Good healing	3/25/30, 3 high voltage treatments	3/18/30, 43	23	150	900	1,050 in 7 days
C. B. 75	Right, 3.5×3 cm.	Slow	Adenopathy	B—	1/29/30, biopsy	Good	1/29/30, 1 high voltage, 2 low voltage treatments	1/29/30, 25	8	160	1,050	1,210 in 9 days
A. M. 61	Right, 3.5×2.5×2 cm.	Moderate	Adenopathy	B	2/11/30, radical mastectomy	Good	12/20/29, 3 high voltage treatments	12/10/29, 29.95	20	125	1,250	1,375 in 10 days
F. V. 64	Left, 4×3.5×3 cm.	Moderate	Adenopathy	B	2/12/30, biopsy	.....	1/31/30, 3 low voltage treatments	2/12/30, 46	18	50	1,565	1,615 in 16 days
C. W. 63	Right, 3×2.5 cm.	Moderate	Adenopathy	B	2/12/30, radical mastectomy	Primary healing	11/21/29, 3 high voltage, 1 low voltage treatments	12/6/29, 30.89	16	125	1,500	1,625 in 25 days
C. S. 67	Left, 6×4.5×2.5 cm.	Rapid	0	B	1/29/30, biopsy	.....	1/28/30, 3 high voltage treatments	1/29/30, 108	36	130	1,800	1,930 in 8 days
M. M. 54	Left, 5×4×3 cm.	Moderate	0	A	8/13/30, radical mastectomy	Secondary healing, dermatitis	12/24/29, 3 high voltage treatments	12/31/29, 74.56	21	100	1,850	1,950
H. S. 72	Left, 3.5×3×1.5 cm.	Moderate	Adenopathy	B	4/9/30, simple mastectomy	Primary healing	1/22/30, 2 high voltage treatments	1/28/30, 46	14	160	1,900	2,060 in 9 days
R. C. 50	Left, 6×6×3 cm.	Moderate	0	A	4/10/30, radical mastectomy	Primary healing	2/24/30, 2 low voltage, 1 high voltage treatments	2/25/30, 111	50	100	2,300	2,400 in 8 days

Axillary Irradiation	Interval Between Irradiation and Operation	End-Results	Gross Pathologic Anatomy	Pathologic Histology
X-rays	5 wk.	No evidence	Tumor, 1×1 cm.	Infiltrating carcinoma simplex, grade 2 radioresistant; vaculolated hydropic viable tumor cells; fibrosis, slough and partial destruction; sublethal dose
X-rays	.....	Regressing	.....	
X-rays	.....	8/12/29, only ¼ former size; 12/6/29, death from cardiac failure	.....	
X-rays	.....	Only slight regression; radioresistant	.....	Intracystic or intraductular adenocarcinoma
X-rays	.....	No evidence	Tumor, 3×3×2 cm.; hemorrhage and necrosis	Infiltrating duct carcinoma; marked changes, in places total destruction; productive fibrosis; squamous metaplasia
X-rays plus 26 mc. in gold seeds	1 mo.	Good to date	Tumor, 5×3×2 cm.; numerous portions necrotic and hemorrhagic	Infiltrating duct carcinoma, grade 2 radioresistant; radium effect focal, leaving some viable carcinoma; axillary nodes are carcinomatous
X-rays	.....	.....	.....	Small cell infiltrating carcinoma; calcification; vascular changes; radiation changes after x-ray therapy
X-rays	7 wk.	Good to date	Tumor, 3×3×1 cm.	Tubular carcinoma of ducts; radioresistant; sclerosis and calcification of vessels; collagen swelling; atrophy and hydrops of tumor cells; productive fibrosis
X-rays plus 27 mc. in 10 gold seeds	.....	Good to date-regression	.....	Two weeks after x-ray therapy, fibrocarcinoma of ducts; radioresistant
X-rays plus 31 mc. in 14 gold seeds	2 mo.	No evidence	Fibrotic mass, 2 cm.	Complete destruction of carcinoma in breast; one node contained atrophied carcinoma
X-rays	.....	No evidence of tumor; no loss of skin	.....	Biopsy before interstitial irradiation; small cell fibrocarcinoma with advanced radiation changes, particularly vascular
X-rays plus 30 mc. in 10 gold seeds	8½ mo.	Excoriation; tumor gone; fibrosis	.....	No residual cancer; evidences of heavy irradiation
16 mc. in 5 gold seeds	10 wk.	No evidence		Biopsy, infiltrating carcinoma; amputated specimen; no evidence of carcinoma
X-rays	6 wk.	.....	Tumor, 3.5×2.5 cm.; myxomatous stroma	Total destruction of all tissues; squamous metaplasia of ducts; small regressing nonviable focus in an area of abortive fibrosis

TABLE 11.—*Patients with Primary Operable Carcinoma of the Breast*

Patient and Age	Location of Tumor, Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Radium Element Pack Treatments	Interstitial, Millicuries	Irradiation, Gold Seeds
C. W. 39	Left, 7×6.5 cm.	Moderate	Adenopathy	B+	10/11/29, radical mastectomy	Secondary healing	8/29/29, 16,000 mg. hr. at 6 cm.	9/12/29, 40.75	13
T. A. 42	Right, 6×4.5×3 cm.	Slow	0	A	9/25/29, radical mastectomy	Secondary healing, necrosis of the edge of the skin	8/12/29, 16,000 mg. hr. at 6 cm.	8/20/29, 33	18
E. S. 53	Right, 8×8×7 cm.	Moderate	Adenopathy	B	Refused	.....	9/12/29, 16,000 mg. hr. at 6 cm.	10/10/29, 77.64	20
N. J. 54	Right, 2.5×2.5 cm.	Moderate	0	A	11/29/29, radical mastectomy	Secondary healing, slight necrosis	8/25/29, 16,000 mg. hr. at 6 cm.; 8/23/29, tray 3,000 mc. hr. at 3 cm.	8/28/29, 12.3	5
E. P. 46	Left, 5.5×3 cm.	Slow	0	B	8/20/29, radical mastectomy	Primary healing	6/1/29, 16,000 mg. hr. at 6 cm.	7/10/29, 41.15	18
F. S. 66	Right, 6×4.75 cm.	Moderate	0	A	1/8/30, local mastectomy	Primary healing	6/4/29, 32,000 mg. hr. at 3 cm.; two areas	7/9/29, 48	22
H. W. 40	Right, 7.5×7 cm.	Rapid	Adenopathy	C	.....	.....	9/20/29, 16,000 mg. hr. at 6 cm.	10/15/29, 85.7	24
E. K. 69	Right, 5.5×3 cm.	Moderate	Adenopathy	B	9/19/29, biopsy	.....	8/23/29, 16,000 mg. hr. at 6 cm.	9/21/29, 50.7	18
M. F. 66	Right, 7×6.5 cm.	Rapid	Adenopathy	B+	2/7/30, radical mastectomy	Seven weeks to heal by secondary intention	10/26/29, 24,000 mg. hr. at 6 cm.	1/17/30, 86	30
E. G. 47	Right, 4.5×4×2 cm.	Moderate	0	B	10/11/29, radical mastectomy	Good healing	8/13/29, 24,000 mg. hr. at 6 cm.	8/31/29, 40	13
M. S. 66	Right, 3.5×3.5 cm.	Moderate	0	A	None, cardiac complications	.....	9/7/29, 16,000 mg. hr. at 6 cm.	9/27/29, 30.36	13
L. E. 62	Right, 6×6×5 cm.	Rapid	Adenopathy	B+	None, diabetic complications	.....	9/11/29, 16,000 mg. hr. at 6 cm.	9/28/29, 72.3	19

Treated by Radium Element Pack and Interstitial Irradiation

Tissue Dosage in Breast, per Cent, Skin Erythema Doses							
Radium Element Pack	Interstitial	Total	Axillary Irradiation	Interval Between Irradiation and Operation	End-Results	Gross Pathologic Anatomy	Pathologic Histology
50	585	635 in 17 days	Radium element pack	1 mo.	No evidence	Softening of tumor	Comedocarcinoma, partly intraductular; tumor cells are atrophic, hydropic and eosinophilic; vessels thrombosed and recanalized
50	600	650 in 9 days	Radium element pack	5 wk.	No evidence	Tumor, 1×1 cm.; fat necrosis; only one small nodule	Infiltrating carcinoma; radiation changes in stroma cells of tumor are markedly atrophic, hydropic and vacuolated
35	865	900 in 30 days	Radium element pack plus 29 mc. in 11 gold seeds	.....	Tumor mass fibrotic, 3.5×3 cm.;skin intact		
100	800	900 in 4 days	0	3 mo.	No evidence	.....	Major portion of carcinoma completely destroyed; few nonviable tumor cells in abortive fibrosis
40	900	940 in 40 days	Radium element pack plus 700 mc. hr. with radium needles	5½ wk.	No evidence	Tumor, 4×2 cm.; half of tumor necrotic	Cellular carcinoma; too necrotic to classify; nonviable cells; only shadow cells; squamous metaplasia of ducts
70	880	950 in 30 days	Radium element pack plus 22 mc. in gold seeds	6 mo.	No evidence; cancer of the tongue	Tumor, 2.5×2.5 cm.; circumscribed	Adenocarcinoma, partially gelatinous; mainly distributed in a peripheral narrow zone about a wide area of radiation fibrosis
45	1,050	1,095 in 38 days	Radium element pack plus 25 mc. in gold seeds	.....	Tumor entirely disappeared in the breast and axilla; metastases to the lung		
50	1,100	1,150 in 30 days	Radium element pack	.....	Complete disappearance of tumor	.....	Infiltrating scirrhous carcinoma on biopsy
70	1,200	Cannot be added	Radium element pack plus 30 mc. in gold seeds	3 wk.	No evidence; radiosensitive	Tumor clinically disappeared after external irradiation	Complete destruction of carcinoma of the breast; one small focus of regressing cells in abortive fibrosis; metaplastic cartilage and bone
90	1,175	1,265 in 19 days	Radium element pack	6 wk.	No evidence	Tumor, 3×2.5 cm.; hemorrhage about tumor	Infiltrating carcinoma; partial total destruction; atrophic regressing tumor cells in one area of abortive fibrosis; mucoid changes
60	1,250	1,310 in 23 days	Radium element pack plus 15.6 mc. in 7 gold seeds	.....	.....	2/3/30, only scar in breast	
50	1,330	1,380 in 18 days	Radium element pack plus 21 mc. in 7 gold seeds	.....	.....	Tumor of the breast gone; new node in right axilla	

On the other hand, a great dosage within certain limits is not incompatible with good wound healing providing the important interval of time between irradiation and operation is maintained.

Case 10, table 10, 1,625 per cent S. E. D. Interval of 42 days.
Case 7, table 9, 1,800 per cent S. E. D. Interval of 68 days.
Case 13, table 10, 2,060 per cent S. E. D. Interval of 70 days.
Case 14, table 10, 2,400 per cent S. E. D. (111 millicuries). Interval of 42 days.

Postoperative External Irradiation.—In the present series of primary operable carcinomas of the breast, we have purposely withheld all postoperative external irradiation in order to evaluate correctly the end-results of preoperative irradiation in measured tissue doses. Prior to these experiments, a routine cycle of roentgen irradiation was given three or four weeks following the operation. By this time the wound had healed, and the patient had recovered sufficiently to undergo treatment without much distress. In our hands, the results have been better when postoperative irradiation has followed surgical intervention than when operation alone has been employed. In general, surgeons have been more willing to submit their patients to postoperative irradiation than to preoperative treatment, in the belief that the likelihood of local recurrence in the operative field was thereby diminished. A continuous follow-up on these patients, month by month, may reveal evidences of recurrence, to which appropriate treatment may be applied. Sufficient data are at hand to prove that postoperative irradiation diminishes the liability to recurrence and prolongs considerably the life of the patient. Yet there are three possible arguments against the procedure: the dosage delivered is insufficient to destroy any viable carcinoma left in the operative field, although it may be instrumental in inhibiting the growth of such cells by enveloping them in dense scar tissue; if a recurrence does appear after irradiation, the intensity of the subsequent treatments must be lessened because of the diminished tolerance of the skin, and carcinomas that have recurred in the face of irradiation probably have an increased radioresistance. The postoperative roentgen treatments are usually given twice a week, with exposure of the same areas used in the preoperative cycle. The dose employed for the supraclavicular and axillary spaces is relatively somewhat heavier than that over the anterior thoracic wall. The breast having been removed, only a superficial dose is necessary over the anterior wall of the chest, whereas for the axilla and supraclavicular regions, a relatively greater depth dose seems indicated. For this reason, high voltage roentgen treatment is given to the axilla and supraclavicular space, and low voltage roentgen treatment to the mammary site on the anterior thoracic wall.

THE PATHOLOGIC CHANGES PRODUCED BY IRRADIATION IN CARCINOMA OF THE BREAST

It is perhaps unfortunate that conclusions on the mechanism of the changes produced by radiation must be derived from a rather heterogeneous material. We have not had a sufficiently large group of cases treated by any one method to enable us to draw conclusions regarding the precise effect of the particular mode of treatment. Patients differ in age and physical status. Carcinoma of the breast is not one disease but a group of diseases, differing in gross anatomy, pathologic histology, radiosensitivity and clinical course. One cannot, for example, compare bulky adenocarcinoma with diffusely infiltrating multiple foci of duct carcinoma. Again, some duct carcinomas are made up of large cells, so large and flattened that they resemble the cells of squamous carcinoma. Others infiltrate widely in small strands of small cells or form masses made up of cells that on superficial examination might be considered lymphosarcoma. Although there are no precise observations on the radiosensitivity of differing types of cancer of the breast, no one who has studied the question of the radiosensitivity of tumors in general can doubt that great differences must exist in the field of carcinoma of the breast. In a group of patients, some treated by roentgen rays alone, some by radium element pack, some by roentgen rays and element pack, some by roentgen rays or radium element pack, or both, combined with interstitial radium emanation, and others by buried emanation alone, with all the varying dosage and time factors, we are far from having a satisfactory experiment even in human biology.

Like all tumors, carcinoma of the breast is subject to many spontaneous changes. Bulky tumors become infarcted; ulceration and infection produce marked changes; thrombosis and obliterative arteritis are spontaneous occurrences; hyaline swelling of the stroma is rather common and, rarely, calcific deposits are found. In other words, many of the changes found to a marked degree in the irradiated tumor of the breast occur to a lesser extent in the untreated or moderately treated case. Therefore, in our cases that have received but small doses by external irradiation one must make a nice distinction between what one regards as the effect of the treatment and the possible spontaneous degenerative processes within the tumors.

Histologic studies seem to indicate that radiation affects tumors (1) by direct influence on the tumor cell and (2) through vascular changes, arteritis, thrombosis or slow vessel occlusion and productive fibrosis. In certain tumors, the direct effect seems most prominent, in others, the second factor. The two modes of action are by no means exclusive, and at the present time no one can say what this so-called direct effect

on the tumor cells is, in what manner it is dependent on alteration of intracellular electrolytes, changes in permeability and the like. The tendency is to assume a direct effect on the tumor cell in tumors in which examination fails to reveal sufficient accessory tissue alterations to account for the disappearance of the disease.

If one were to attempt an estimation of the radiosensitivity of carcinomas of the breast, one might list them in the order of increasing sensitivity somewhat as follows, acknowledging, however, that sufficient observations in the radiosensitivity of carcinoma of the breast are not

TABLE 12.—*Patients with Primary Operable Carcinoma of the Breast Treated by*

Patient and Age	Location of Tumor, Size	Rate of Growth	Axilla	Clinical Index of Malignancy	Operation	Healing of Wound	Roentgen Treatments	Radium Element Pack Treatments	Interstitial Millicuries	Irradiation, Gold Seeds
K. S. 65	Left, 5×4.5 cm.	Rapid	Adenopathy	B+	0	.....	2/8/28, 2 high voltage treatments	2/13/28, 8,000 mg. hr. at 6 cm.	.....	..
M. C. 49	Right, 6×5.5 cm.	Slow	Adenopathy	B—	12/29/28, radical mastectomy	Good healing	2/24/28, 2 high voltage treatments	3/7/28, 16,000 mg. hr. at 6 cm.	.....	..
H. N. 79	Left, 5×4.5 cm.	Slow	Adenopathy	B—	0, age	.....	6/25/29, 3 high voltage treatments	8/8/29, 16,000 mg. hr. at 6 cm.	8/17/29, 22.4	10
B. H. 34	Right, 8×5×3.5 cm.	Rapid	Adenopathy	C	11/29/29, radical mastectomy	Incomplete closure graft	5/29/29, 3 high voltage treatments	6/10/29, 32,000 mg. hr. at 6 cm. over two areas	10/17/29, 89.1	22

available: (1) sclerosing fibrocarcinoma, (2) large cell infiltrating duct carcinoma (carcinoma simplex), (3) small cell infiltrating duct carcinoma (carcinoma simplex), (4) solid medullary carcinoma, (5) intraductular comedocarcinoma, (6) intracystic adenocarcinoma, and (7) certain very small cell carcinomas superficially resembling lymphosarcomas.

Increasing anaplasia within the individual groups increases the sensitivity. Ewing has said: "Carcinomas are resistant in inverse proportion to the degree of anaplasia and in direct proportion to the amount of desmoplastic reaction which they excite." Sensitivity is altered by the clinical setting. Anemia and cachexia decrease sensitivity; inflammatory characteristics (acute inflammatory carcinosis) increase it. The gelatinous character of the colloid carcinomas of the breast prevents an adequate reaction of the tissues to irradiation. The large intracystic

adenocarcinomas owe their radiosensitivity to their rapid growth, especially to their unstable vascularity, which accounts for the frequent bulky necrosis of these tumors following irradiation. In other words, we are dealing with a complex problem, with facts difficult of statement and ascertainable only by experience.

Radiosensitivity is in no sense an exact criterion of the ultimate ease of cure (even though local cures are affected), because these more cellular tumors usually metastasize more readily and widely. The well known law of Bergonie and Tribondeau established the definite relation-

Combinations of Roentgen Rays, Radium Element Pack and Interstitial Irradiation

Tissue Dosage in Breast, per Cent, Skin Erythema Doses								
X-Rays	Radium Element Pack	Interstitial	Total	Axillary Irradiation	Interval Between Irradiation and Operation	End-Results	Gross Pathologic Anatomy	Pathologic Histology
110	30	...	140 in 15 days	X-rays	.....	11/28, died		
125	60	...	185 in 12 days	X-rays	9 mo.	3/30, tumor of the breast was 2 cm. in diameter; 11/30, no tumor present	Necrotic tumor mass, 4.5×3 cm.	Adenosarcoma; degenerated; hemorrhage; metastases to lymph node were carcinomatous
140	50	550	740 in 2 mo.	X-rays plus radium element pack plus 15 mc. in gold seeds				
80	70	1,000	Cannot be added	X-rays plus 24.5 mc. in gold seeds	6 wk.	.....	Softened tumor; calcification; hemorrhage in tumor	Infiltrating comedocarcinoma; hyaline stroma; productive fibrosis; squamous metaplasia of ducts; marked swellings and degeneration of tumor cells

ship of the grade of malignancy to the degree of radiosensitivity. Moreover, some mammary cancers have periods of apparent latency with later resumption of activity; the radiosensitivity of such a cancer fluctuates with its growth proclivities. Our experiment has been based on the assumption that true radiosensitivity is proportional to the spatial dose of rays absorbed necessary to sterilize the cancer. We possess no method of estimating the dose of rays actually absorbed by the cells of any tumor, but we can determine with some degree of accuracy the amount of irradiation delivered to the cells of the tumor necessary to effect their destruction.

The nature of the tumor bed is an important factor in radiation therapy for carcinoma of the breast, because the fatty envelope retards the response to treatment. This fact alone accounts for the seeming

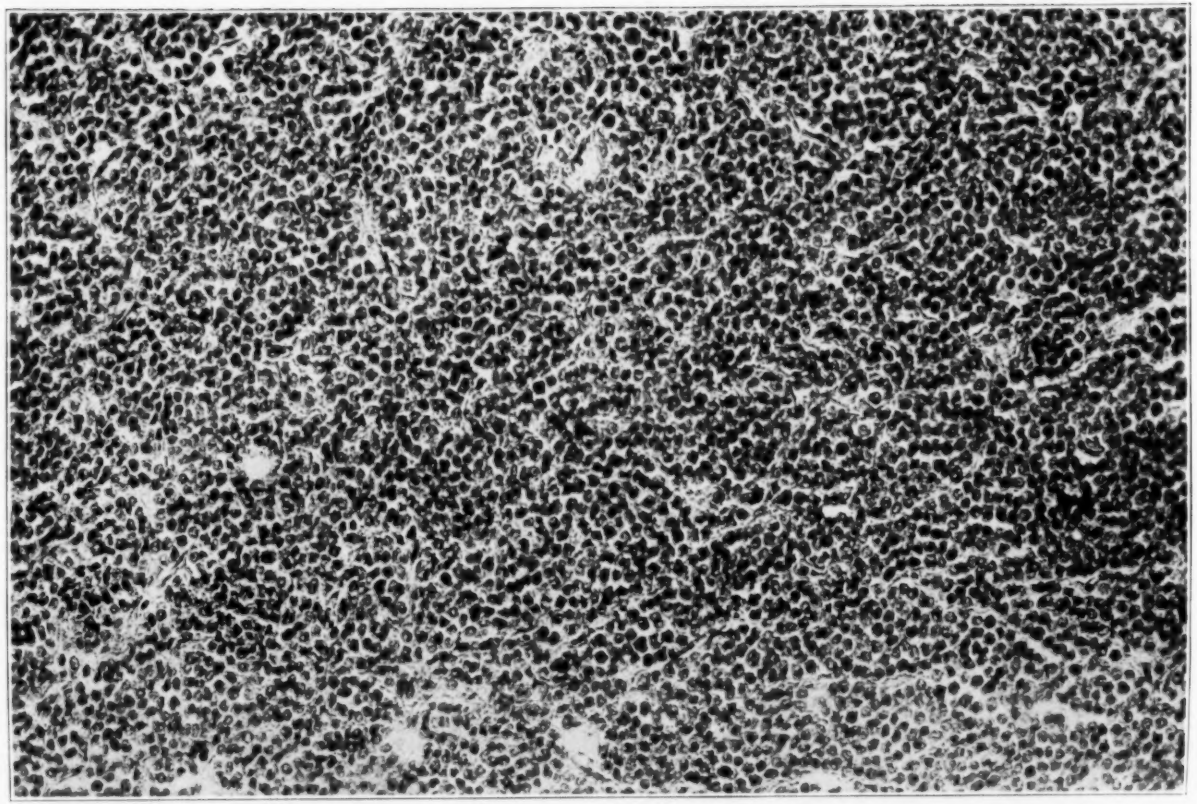

Fig. 13.—Area of diffuse small cell carcinoma; the cells resemble those of lymphosarcoma; other areas in this tumor, more radioresistant, showed tubular and alveolar carcinoma, grade 4; marked radiosensitivity; rare type.

Fig. 14.—Solid alveolar duct carcinoma. The cells were relatively large. Radioresistant; grade 2.

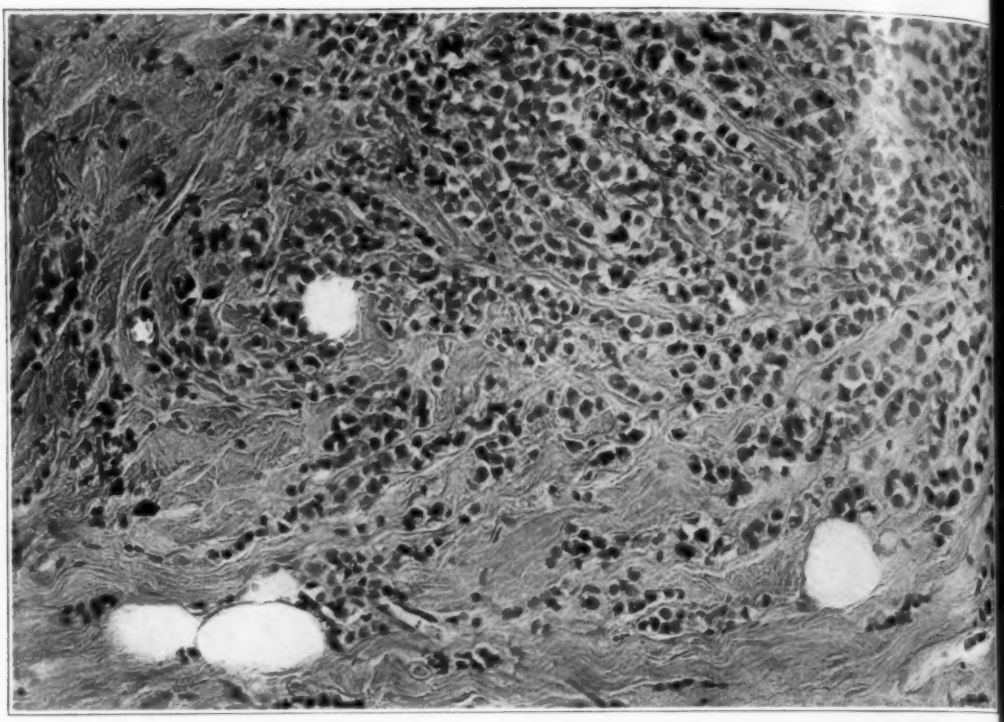

Fig. 15.—Small cell infiltrating duct carcinoma, grade 3. Other areas of this tumor showed a diffuse growth resembling lymphosarcoma. Relatively radioresistant type.

Fig. 16.—Comedocarcinoma infiltrating diffusely. The comedo areas were relatively radiosensitive and the balance of the tumor was radioresistant; grade 2.

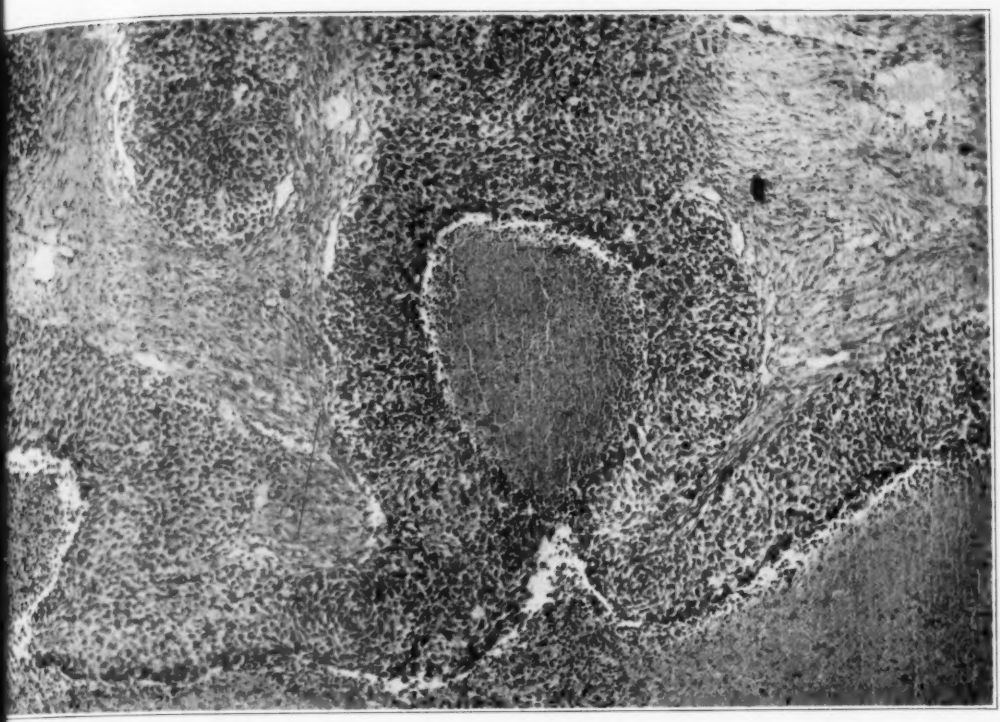

Fig. 17.—Bulky adenocarcinoma (medullary carcinoma) showing a tendency to spontaneous necrosis; blood supply was unstable. Relatively radiosensitive, owing to the readiness with which blood supply was interfered with by irradiation.

Fig. 18.—Intracystic papillary adenoma malignum, relatively radiosensitive on account of papillary structure. Clinically, the lesion was essentially benign.

great radioresistance of many mammary cancers. Ewing has said that, "Fat tissue with the low metabolism of fat deposits is highly resistant to radiation, but after heavy dosage, the cell membranes rupture, minute oil cysts form, saponification occurs, new blood vessels appear, and there is considerable proliferation of the fat cells which are difficult to destroy when invading fat tissue." This fact has stimulated us to use larger and still larger doses of interstitial irradiation in the breast in an attempt to improve the tissue reaction by inducing fat necrosis, the infiltration of

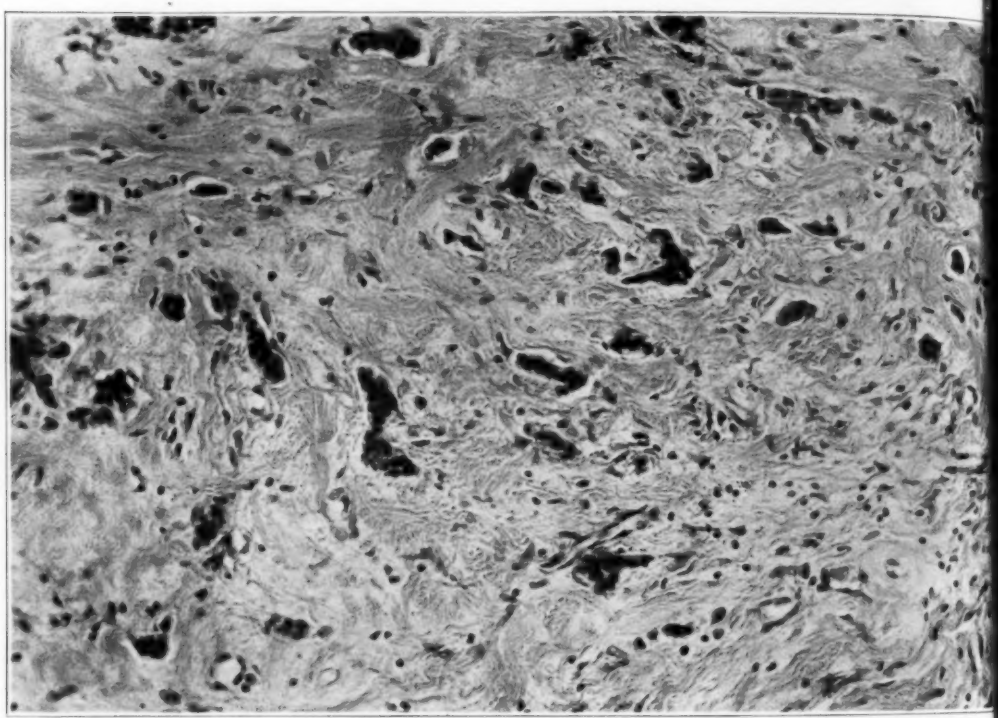

Fig. 19.—Radioresistant fibrocarcinoma (scirrhous), grade 2.

plasma cells and leukocytes, the augmentation of blood supply and the formation of granulation tissue in the neighborhood of the cancer.

Acquired Radioresistance.—It is probable that an immunization of the neoplasm results from the administration of repeated and long-spaced sublethal irradiations. Hence, there is a progressive diminution in radiosensitivity under the influence of repeated inadequate treatments with radium. Possibly the more radioresistant cells of successive generations are those which persist after these repeated treatments, and thereby are selectively culled from the original tumor after the manner of selective breeding. For very advanced cancers, in which the administration of a

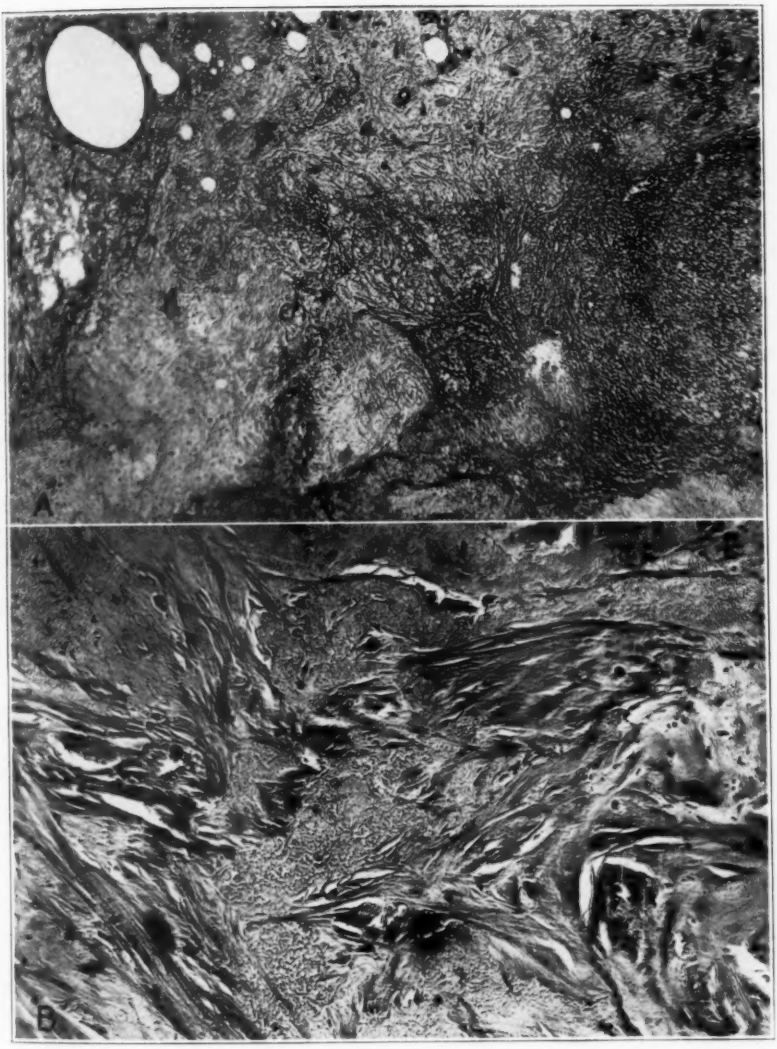

Fig. 20.—*A*, complete necrosis of tumor, showing fibrin, capillary necrosis and inflammation of fat tissue. *B*, fibrosis; foci of calcific deposit at the site of the destroyed tumor cells.

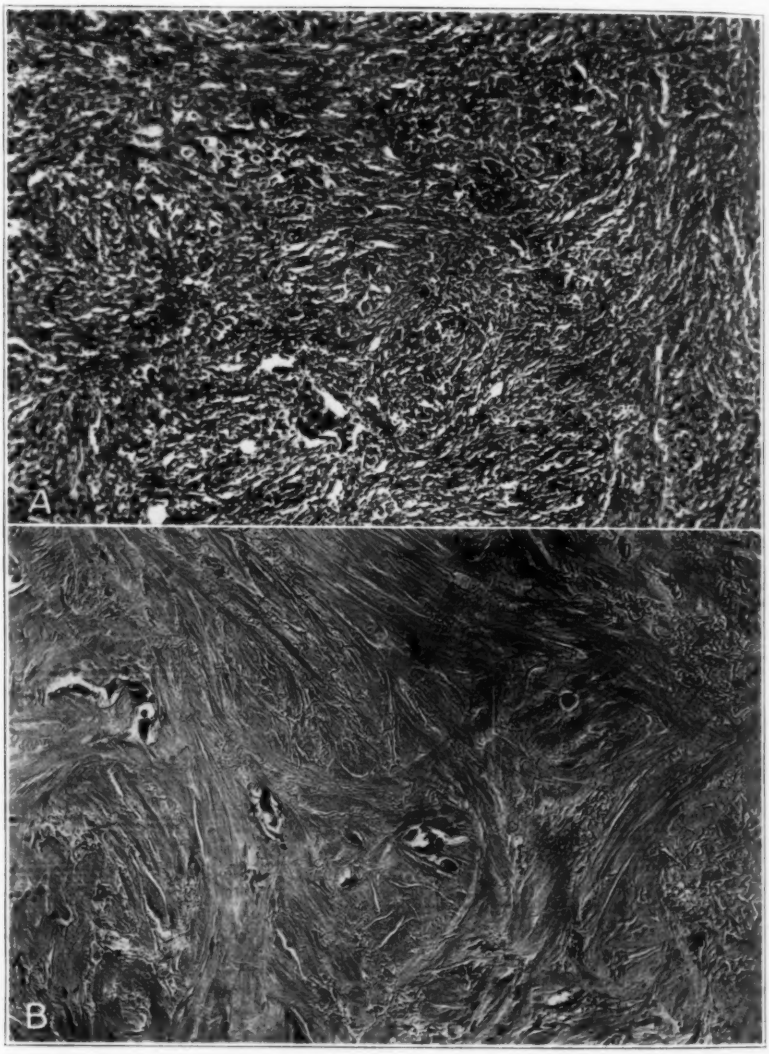

Fig. 21.—*A*, regression of atrophic, hyperchromatic tumor cells in the midst of extreme productive fibrosis. *B*, productive fibrosis, abortive fibrosis and atrophic tumor residua.

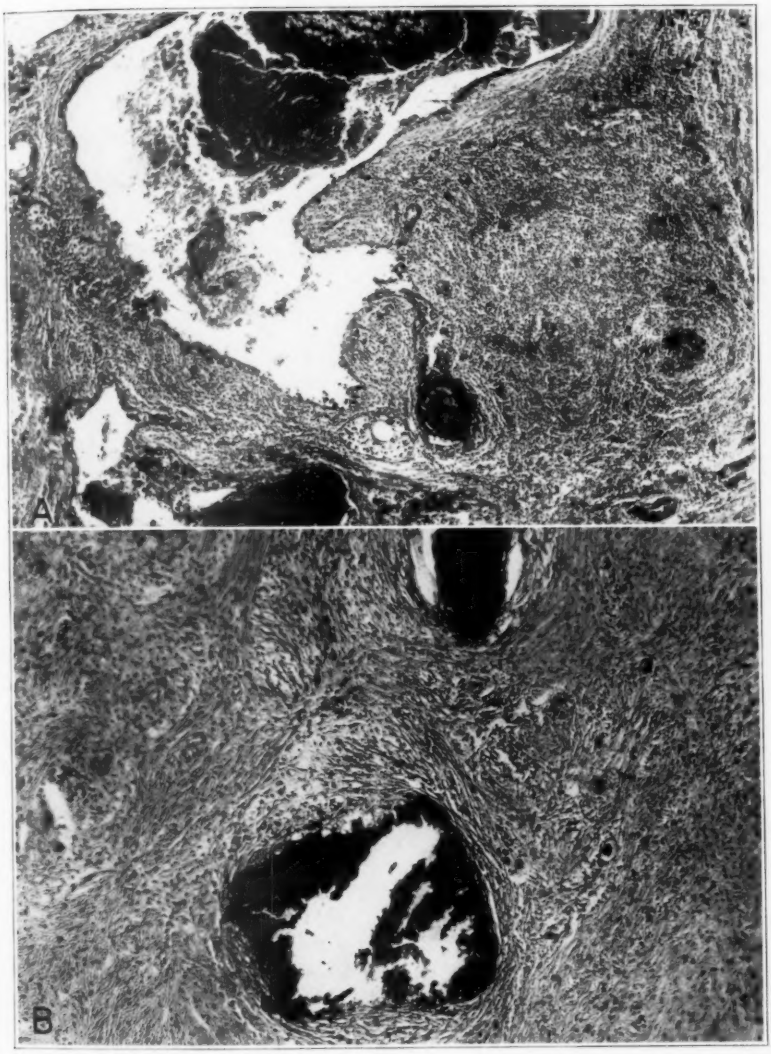

Fig. 22.—*A*, sloughing and calcification in comedocarcinoma, with marked lymphocytic infiltration. *B*, calcific deposits in sloughing comedocarcinoma.

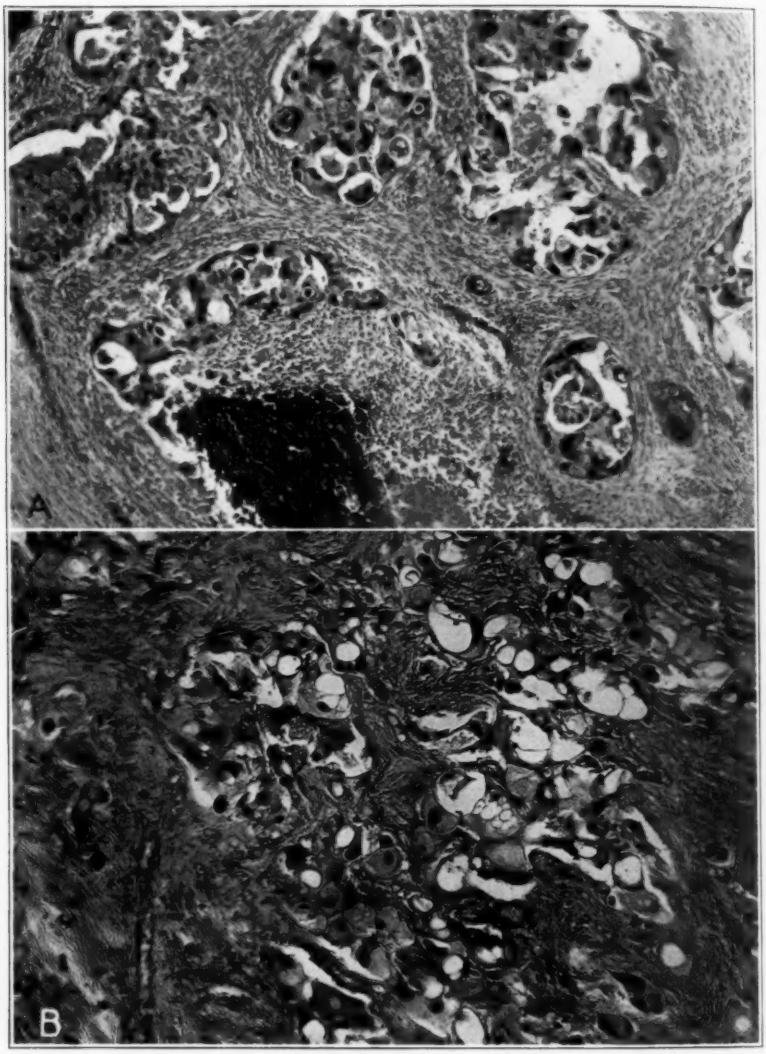

Fig. 23.—*A*, sloughing comedocarcinoma, showing large, hydropic, squamous-like cells, with giant, degenerative nuclei. Earlier stage of calcification in area of hemorrhage, sloughing and accumulation of fatty endothelial leukocytes. *B*, regression of carcinoma, with squamous metaplasia, degenerative hyperchromatism and extreme hydropic changes.

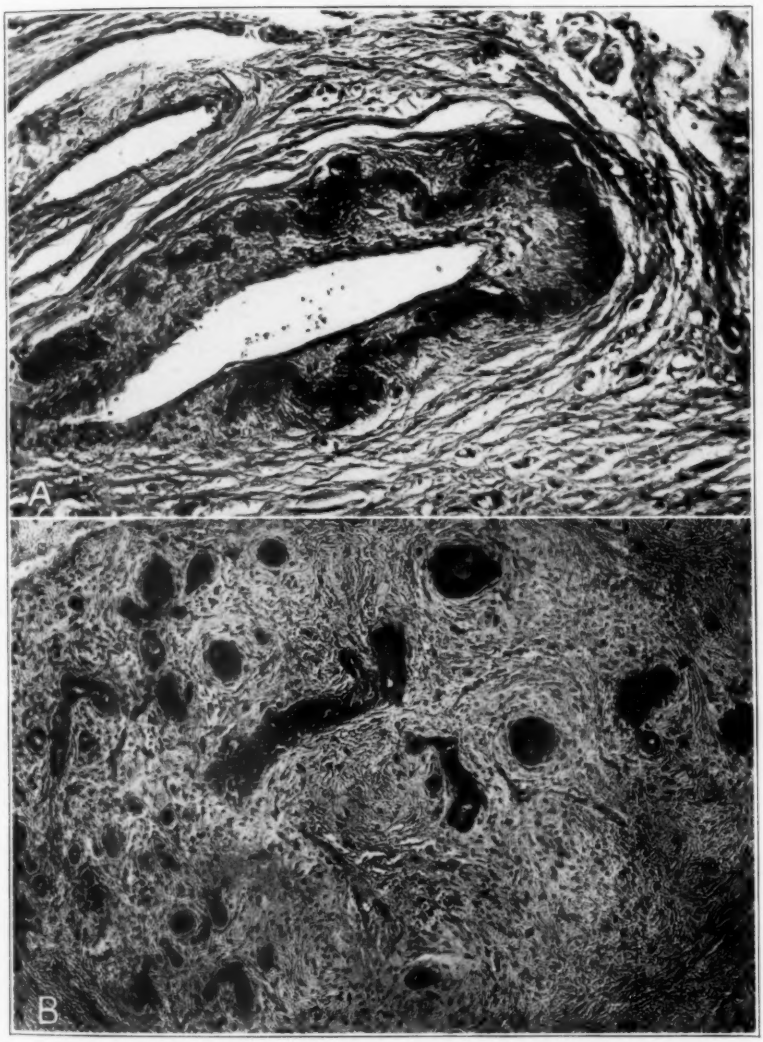

Fig. 24.—*A*, calcific vascular deposit following external irradiation. *B*, squamous metaplasia in normal areas of the breast adjacent to the tumor which had been interstitially irradiated.

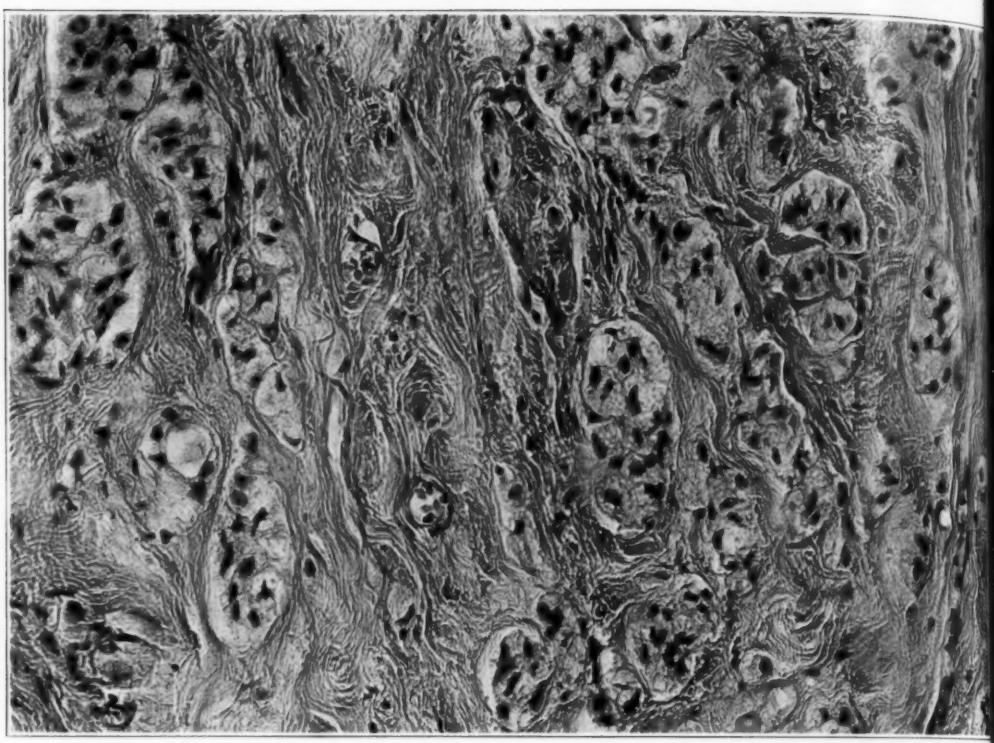

Fig. 25.—Photomicrograph of a mammary cancer that had received 350 per cent of a skin erythema dose of radium. Note the carcinoma cells.

Fig. 26.—Whole section of breast with an untreated bulky adenocarcinoma which involved the skin and the muscle.

large dose of irradiation is dangerous, one may purposely employ fractionation and espacement of doses, which result in only temporary palliation. Radioresistance is not an instantaneously acquired but a latent property of cancer tissue. It is not easily produced by the administration of a small dose of radium; it is not manifested immediately after the administration of a strong dose of irradiation. The radio-immunization may occur after a single intensive treatment or after a series of irradiations with fractionation of the dose. It is after a delay of from six weeks to two months that the phenomenon becomes apparent, and it attains its maximum even later. Once acquired, this radioresistance persists indefinitely. At the same time that the neoplastic tissue is becoming refractory to radium or roentgen rays, the general tissues (connective tissue, blood vessels) are rendered incapable of supporting a new cycle of radium or roentgen treatment without great danger of necrosis. Tumor restraint rather than destruction is obtained in this manner. These dormant cancer cells lying in indolent foci in beds of scar tissue, retain enough vitality to grow again when sufficient provocation occurs. The reappearance of cancer in the irradiated field presents a difficult problem in treatment, owing to this acquired radioresistance. "Abortive fibrosis" is a term that Ewing has applied to a form of indolent fibrosis with destruction of all tissue cells and most blood vessels, but with persistence of tumor cells. Even in the breast, he found wide hyaline strands of fibrous tissue enclosing groups of well preserved tumor cells, which maintain their nutrition through scanty but rigid sinusoid blood vessels. Ewing believed that these tumor cells acquired an increased radioresistance greater than that of the normal tissues, and that this condition results more often after radium than after roentgen treatment. Although the desired attainment in the case of advanced inoperable mammary cancers, the discovery of abortive fibrosis in a breast with a condition classified as primary operable carcinoma is proof of improper or insufficient irradiation.

Changes Produced by Measured Tissue Doses of Irradiation.—In reviewing sections from carcinomas of the breast treated by high voltage roentgen rays or by element pack alone, certain facts seem apparent. In two patients receiving 100 and 110 per cent of skin erythema doses in the tumors, the changes produced were negligible. In the second case, a portion of the tumor had undergone regression and showed local areas of abortive fibrosis resulting from vessel occlusion. There was considerable calcification, but the patient had a slowly growing tumor and was 71 years old. Probably the calcification was a spontaneous change. One hundred and thirty per cent of skin erythema doses of roentgen rays in one patient produced slight atrophy of the tumor cells within one month, and in a second case caused complete regression of a radiosensitive carcinoma—one of the rare, unexplained cases undoubtedly car-

cinoma but of unknown type. Three tumors receiving doses of 140 per cent showed insignificant changes in ten days, some productive fibrosis in three weeks, but considerable atrophy with sloughing and calcification in two months. This might suggest that the effects increase with the interval of time between treatment and amputation, but, unfortunately, we have no basis for conclusions from these three cases, since they comprised three different tumor types: a gelatinous carcinoma, a bulky adenocarcinoma and a moderately small cell duct carcinoma. Two tumors treated with element pack alone disappeared completely. Again, unfortunately, we do not know the type of tumor. Two patients receiving 40 and 50 per cent S. E. D. into the tumor mass, followed by amputation three and four weeks later, showed no significant tissue changes. One patient received 40 per cent, and at amputation five weeks later the tumor cells were swollen and hydropic, or atrophic with the stroma much swollen. A fourth breast receiving 85 per cent and amputated two months later showed swollen, hyalinized stroma, hydrops and atrophy of the tumor cells, many acidophilic tumor cells with degenerative, giant nuclei. A wide focus of necrosis and fibrosis had resulted from vascular occlusion. Although it is difficult to be certain, we gain the impression that the smaller tumor doses from the radium element pack are slightly more effective than larger doses of roentgen ray. Save for the rare, unexplained, total disappearance of tumor masses, it is obvious that the doses deliverable by external radiation alone have been quite inadequate in controlling the disease.

Adequate interstitial radiation, when properly placed, completely alters the anatomy of the tumors. Complete destruction may occur and does occur with the larger doses. The tumors soften, and the lesions assume more nearly the appearance of a fibrous mastitis. Often the tissue is glistening and gelatinous. It may be difficult to tell by palpation where the tumor ends and the fibrous mastitis begins. About the seeds are areas of yellow, opaque, granular, necrotic material often infiltrated with blood. The fatty tissue undergoes necrosis. Bulky adenocarcinomas slough within their capsules. Even when total destruction does not occur within the time elapsing between interstitial radiation and amputation, the tumors shrink markedly. Histologically, the pictures are variable. Some tumors vanish, leaving only wide areas of necrosis with hemorrhage, acute necrosis of vessels, collagen, tumor and fat—shadows of the original disease. The anatomic picture indicates that these are the more cellular adenocarcinomas and medullary carcinomas. The infiltrating duct carcinomas with moderate or large amounts of stroma are more resistant and disappear by progressive atrophy. Their cells are often hydropic and undergo a type of squamous metaplasia preceding necrosis. Swelling occurs in the connective tissue, proliferation may be marked, and the end-result may be abortive fibrosis or minute calcific

masses in the dense hyaline connective tissue. Lymphocytic infiltration may be prominent but may not be attributable to the treatment. Comedocarcinomas undergo from moderate to extreme squamous metaplasia and then apparently slough. With the sloughing, the lumina become filled with fatty débris, fatty leukocytes and blood pigment. Particularly with this fatty accumulation, calcific deposits result. Vascular changes are acute; the chronic slow sclerosis following roentgen irradiation does not occur, although this is seen in cases in which combined external and interstitial radiation is used. Squamous metaplasia of the surrounding lobules of the normal breast occurs regularly after interstitial radiation.

After surveying sections from amputated breasts, either by the study of several sections from each tumor or by large sections after the method of Cheatle, the following tumor doses administered by interstitial irradiation alone or by combinations with element pack or roentgen rays were regarded as lethal: 900 (two cases), 940, 1,095, 1,150, 1,165, 1,200, 1,265, 1,300, 1,310 (two cases), 1,380 (two cases), 1,625, 1,800, 1,930, 1,950, 2,060 and 2,400 per cent. Results regarded as questionably lethal (cells remaining, but of doubtful viability) were obtained after doses of 1,020, 1,265, 1,350 and 1,500 per cent. What might have happened to the remaining cells had more time elapsed between irradiation and amputation can only be surmised. The breast that showed questionably viable elements after a dose of 1,500 per cent was amputated four weeks after interstitial irradiation. Definitely sublethal results were obtained with doses totaling 635, 650, 760, 950, 1,000, 1,050 and 1,375 per cent. In the case of the failure with 1,000 per cent and 1,050 per cent doses, the tumors were large, measuring 3.5 by 5 by 8 and 5 by 5.5 cm., respectively. There is little doubt that the failure may be properly ascribed to the difficulties in the accurate seeding of such large tumors. The failure of the 1,375 per cent dose must be due to technical errors since the tumor was not large; there is grave reason to doubt that a properly placed dose as high as 900 per cent will not destroy a cancer of the breast.

An attempt to tabulate the histologic changes following external and interstitial irradiation may be summarized as follows. The difficulty is that the dosage obtained by interstitial irradiation cannot be approached by external irradiation alone. The summary therefore is not a comparison between the effects of two types of irradiation but between two types and two widely different degrees of dosage.

External Irradiation

1. Mainly a vascular change
2. Moderate hydropic swelling of tumor cells
3. Moderate atrophic degeneration

4. Marked collagen swelling
5. Productive arteritis with thrombosis
6. Calcific deposits in vessel walls
7. Productive fibrosis

Interstitial Irradiation

1. Mainly a direct effect on the tumor cell
2. Ballooning degeneration
3. Hydropic swelling

Fig. 27.—Whole section of a breast involved by mammary cancer, which had been given preoperative external and interstitial irradiation. The tumor was completely necrotic. The small black areas represent persistent ducts lined by squamous metaplastic cells.

4. Giant nuclei and atypical degenerative mitoses.
5. Tendency toward squamous metaplasia followed by sloughing
6. Hemorrhages, infiltration by fatty macrophages with ensuing extensive calcific deposits
7. Acute capillary necroses with resultant tumor necroses
8. Squamous metaplasia of the normal, adjacent lobules of the breast
9. Collagen swelling, productive fibrosis and late atrophy of the residual tumor

Cancer cells may recover from some nuclear damage, as can be witnessed by the late resumption of growth, but when pyknosis, hydrops and karyorrhexis occur in pronounced form, the immediate or eventual death of the cell is assured.

B. PRIMARY INOPERABLE CARCINOMA OF THE BREAST

All patients with malignant neoplasms of the breast who apply to the Breast Clinic of the Memorial Hospital are classified and assigned to one of several groups, named in the descending order of frequency: recurrent inoperable, primary inoperable, primary operable and recurrent operable carcinomas of the breast. An additional group, termed "prophylactic," is made up of postoperative patients without clinical evidence of cancer, who have been referred for irradiation to the breast wound and drainage areas. The criteria of inoperability are: (1) definite fixation of the tumor to the thoracic wall; (2) marked involvement of the axillary nodes on the same side as the breast lesion, with extension well up beneath the clavicle; (3) definite fixation of the axillary nodes to the thoracic wall; (4) well marked fulness of the supraclavicular region of the involved side; (5) palpable supraclavicular nodes; (6) firm nodes easily palpable in the opposite axilla or the opposite supraclavicular space; (7) evidence of metastasis in the other breast; (8) diffuse extensive invasion of the skin with or without cutaneous nodules; (9) evidence of metastasis to the pleura, lungs or mediastinum; (10) evidence of metastasis to the bones, and (11) metastasis to distant organs, such as the liver, the brain, etc.

The futility of surgical intervention as a curative measure for these advanced carcinomas is manifest. The only possible sphere for operation in the management of these primary inoperable cases lies in the palliative operation (simple mastectomy) after adequate irradiation. Such an operation is indicated when ulceration is present or imminent, or when the bulk of the tumor is distressing to the patient. Following such a removal and the subsequent skin-grafting, roentgen treatments are given when indicated.

Irradiation is now generally regarded by the medical profession as the only worth while method in the treatment for primary and recurrent inoperable carcinomas of the breast. We are justified in believing that when a large portion of the active disease is made stationary or regressive, the patient will be better able to combat the other metastatic lesions. In the event that the cancer is so extensive as to be obviously incurable, irradiation should not be too vigorous, else the bodily resistance to the disease may be greatly lowered. External irradiation has been the procedure of choice in the treatment for these cases during past years; it

is still the only possible means in the treatment for metastases to the bones, lungs, brain and skin. So long as the tumors in these locations continue to regress, further irradiation is withheld. Another series should never be given solely because the skin is in a condition to tolerate it. On the other hand, a second series of treatments (roentgen rays or radium element pack) may be given at the end of six weeks if no definite change has taken place in the tumor or it has ceased to regress, and providing the patient's general condition remains satisfactory.

One important reason for accepting cases of advanced mammary cancer for radiation treatment lies in the fact that occasionally a case of this type may give a far better result following palliative irradiation than one could have hoped for when the patient was first seen. We recently performed a necropsy on a woman who had been kept alive for six and one-half years by the proper palliative irradiation of an inoperable mammary cancer. Another patient, aged 56, had an enormous tumor, 14 by 12 by 10 cm., situated in the axillary tail of the left breast. The microscopic diagnosis was carcinoma. Large, soft, discrete lymph nodes were also palpated in the left supraclavicular space. Six weeks later, following one cycle of treatments by the 4 Gm. radium element pack at 6 cm. distance for 16,000 milligram hours to each area, the supraclavicular nodes had disappeared, and the primary carcinoma had diminished until only a small nodule less than 2 cm. in size remained; interstitial irradiation will be given. Fortunately, the more rapidly growing and early metastasizing carcinomas are usually radiosensitive in similar degree, which accounts for these favorable responses in seemingly hopelessly advanced cases.

Some of the patients with the acute inflammatory type of mammary cancer do very well for a considerable period following appropriate irradiation. The explanation for the failure of surgical intervention lies in the diffuse invasion of the dermal lymphatics. Almost any line of incision passes directly through invaded lymphatic vessels and venules with no barrier to prevent immediate recurrence or wide dissemination.

Whenever inoperability is due to fixation of the primary tumor to the thoracic wall or to the state of the axillary nodes, we employ the same procedure in radiation treatment as obtains for the primary operable mammary cancers, namely, external irradiation followed by interstitial irradiation in properly measured dosage (table 13). The method constitutes the nearest approach to the successful treatment for inoperable mammary cancers, and is handicapped only by the inaccessibility of metastases in the liver, lungs and bones. The delivery of proper tissue doses of irradiation by interstitial means, for the first time affords the hope of curing certain inoperable carcinomas of the breast.

Localized shotty subcutaneous nodules in the thoracic wall are treated first by blanket external irradiation and then by the implantation of gold radon seeds of from 1 to 2 millicuries in strength beneath these nodules. A barrage of these gold seeds is sometimes placed around or in advance of progressive cutaneous metatases or extensions.

Complete dissection of the supraclavicular area to remove metastases in nodes cannot be done without divison of the clavicle, which seems a surgical measure not to be recommended because there are probably extensions of the disease beyond the supraclavicular area. Likewise, the presence of axillary nodes with extension well up behind the clavicle is the precursor of supraclavicular involvement. Interstitial irradiation of the supraclavicular nodes even when they are surgically exposed, is sometimes attended by an intractable neuritis, which may persist for many months. The introduction of gold seeds into these nodes must be done cautiously, and the dose must be less per cubic content of tissue than for metastases in the axillary lymph nodes. Repeated external irradiation of the supraclavicular space, even when no palpable disease is present in this location is followed by an immediate puffiness and a later fibrous formation which obliterates the fossa and simulates the presence or persistence of cancer.

Metastasis to the sternum is of frequent occurrence. Our experience indicates that this localization of metastatic mammary cancer is favorable, because of the effectiveness of radiation therapy. One patient has remained well for six years, and another patient presents no evidence of recurrence four years after external irradiation to sternal metastases which appeared subsequent to mastectomy. We can offer no explanation for the relative radiosensitivity of mammary cancer metastatic to the sternum. Radium seems to be more effective than roentgen rays in the treatment for these lesions.

The irradiation of metastases to bone serves three purposes; it may cause an immediate subsidence of pain; it may induce a partial regression of the metastatic carcinoma, and it may stop destruction of bone. When properly administered treatments by radium or roentgen rays are given to these metastases, the reparative osteogenesis often proceeds without delay. In fact, pathologic fractures through metastatic bone lesions from primary mammary cancer can heal with good formation of callus, following these treatments, a phenomenon also observed for the pathologic fractures of certain primary tumors of the bone, such as the endothelial myeloma of Ewing and the benign giant cell tumor. A patient who presents multiple or disseminated metastases to bone obtains a greater regression in these metastatic lesions by irradiation than one who presents a single metastasis to bone. The reason for this difference is that the type of tumor that metastasizes widely to several bones is usually a cellular, anaplastic, small cell, radiosensitive carcinoma.

TABLE 13.—*Measured Tissue Dosage in the Irradiation of Primary Inoperable Carcinoma of the Breast*

Patient and Age	Size	Axillary Adenopathy	Cause of Inoperability	Operation	Roentgen Treatments	Radium Element Pack Treatments	Interstitial Treatments	Tissue Dosage in Breast, per Cent, Skin Erythema Doses: X-Rays	Radium Element Pack	Interstitial	Total	Other Irradiation	End-Results	Pathologic Histology
S. G. 46	9.5×7.5 cm.	+	Metastases to skin	1/15/30, local mastectomy	12/23/29, 2 high voltage treatments	9/20/29, 16,000 mg. hr. at 6 cm.	.....	65	25	...	Cannot add	Axilla and supraclavicular region by x-rays and radium element pack	10/30/30, died	Infiltrating carcinoma of the sweat gland; productive fibrosis; hydropic degeneration and acidophilic changes in tumor cells; vascular lesions
A. M. 44	5.7×3 cm.	+	Supraclavicular node	6/15/28, local mastectomy	5/4/28, 2 high voltage treatments	.....	.....	140	..	...	140	6/15/28, right axilla 23.4 mc. in gold seeds	4/12/30, metastases to the lung; tumor in breast, 2×2 cm.	Five weeks after irradiation, carcinoma simplex, grade 2 radioresistant; much necrosis and fibrosis
B. C. 58	Right, 8×6 cm.	+ +	Bilateral tumors in breasts	10/12/28, right local mastectomy	2/24/28, 2 high voltage treatments	.....	.....	90	..	...	.....	Axilla by high voltage x-rays	5/26/30, died	Right breast, dense fibrosis, sclerosis of vessels, no tumor; left breast, abortive fibrosis, strands of carcinoma in scar tissue
	Left, 7×5 cm.	+		3/29/29, left local mastectomy	1/21/29, 2 high voltage treatments	.....	.....	155						
L. H. 52	8×5.5 cm.	+	Supraclavicular node	.....	8/1/29, 4 high voltage treatments	6/14/29, 16,000 mg. hr. at 6 cm.	.....	150	40	...	190 in 2 mo.	Axilla by x-rays; supraclavicular space by radium element pack	Tumor uncontrolled; 12/8/29, died	
H. N. 52	2.25×1 cm.	+	Supraclavicular node	6/1/28, local mastectomy	5/2/28, 3 high voltage treatments	.....	.....	225	..	...	225 in 12 days	Left axilla by x-rays and radium element pack; 20 mc. in gold seeds	1930, no evidence except pain in axilla	Three weeks after irradiation; large cells in last stage of regression; infiltrating carcinoma
A. B. (O) 55	4.5×4 cm.	+	Supraclavicular nodes	4/13/28, local mastectomy	11/11/27, 3 high voltage treatments; 1/7/28, 2 high voltage treatments	....	....	150 120	..	...	270	Axilla and supraclavicular region by x-rays and 31 mc. in gold seeds	6/24/29, died	Small cell alveolar carcinoma simplex invading lymphatics; wide fibrosis; viable tumor cells

M. S. 49	4×3× 2 cm.	+	Metastasis to lung	1/3/30, local excision	6/7/29, 2 high voltage treatments	6/10/29, 16,000 mg. hr. at 6 cm.	6/3/29, 10 mc. in gold seeds	150	90	350	500 in 7 days	Chest and axilla by x-rays	No evidence of tumor in breast; metastases to chest larger	Four months after irradiation; infiltrating duct carcinoma, mostly gelatinous
R. R. 51	9×8 cm.	+	Metastasis to bone and lung	.....	.....	.....	9/6/29, 76.28 mc. in 29 gold seeds	...	..	700	700	X-ray pelvic cycle; left axilla by radium element pack plus 40 mc. in gold seeds	Tumor of breast diminished one-half in size by 11/20/29; 9/17/30, died	
E. L. 60	4×3.5 cm.	+	Metastasis to spine and pelvis	.....	7/12/29, 3 high voltage treatments	.....	7/24/29, 25.4 mc. in 11 gold seeds	140	..	560	700	Axilla, spine and pelvis by x-rays	10/13/30, no evidence in breast or axilla; metastases inactive	
E. P. 48	2 masses 4.5×2.5 cm. and 2.5× 2.5 cm.	0	Metastasis to lung	Biopsy after irradiation	.....	.....	11/7/29, 42.4 mc. in gold seeds (as 3 spheres)	...	..	900	900	11/7/29, 28.4 mc. in gold seeds in right axilla	Tumor almost completely gone; gain in weight	Biopsy after irradiation; few isolated hyperchromatic cells in dense scar tissue
E. H. 64	6×6 cm.	+	Supraclavicular node	Biopsy before irradiation	7/29/29, 1 high voltage treatment	4/27/29, 16,000 mg. hr. at 6 cm.	10/5/29, 45.6 mc. in 19 gold seeds	75	50	850	Cannot be added	Left axilla by x-rays and radium element pack plus 45.4 mc. in gold seeds	Regression; tumor smaller; disease inactive	Biopsy before irradiation; infiltrating carcinoma, small cells, grade 2 plus radiosensitive
S. M. 45	10×9× 5 cm.	0	Metastasis to lung	2/7/30, local mastectomy	.....	.....	1/10/30, 99.5 mc. in 42 gold seeds	...	..	1,000	1,000	Left axilla by 20 mc. in 12 gold seeds	Sloughing wound; note short interval between irradiation and operation	Fibrosarcoma
B. K. 67	5.5×4 cm.	+	Diabetes nephritis	Biopsy before irradiation	.....	.....	10/11/29, 47.5 mc. in 25 gold seeds	...	..	1,000	1,000	Right axilla by 9.7 mc. in 6 gold seeds	No evidence (5/12/30); scar in breast; recurrence in axilla (7/23/30)	Biopsy before irradiation; small cell infiltration carcinoma, duct type, radiosensitive
C. R. 68	4×2.5 cm.	0	Metastasis to bone and lung	9/24/29, biopsy	6/4/29, 3 high voltage treatments	.....	9/24/29, 27 mc. in 10 gold seeds	140	..	960	1,100 in 1 mo.	Right axilla by x-rays	Epidermicidal dose; no evidence of cancer	Biopsy after external irradiation; fibrocarcinoma
A. S. 58	5.5×4 cm.	+	Infraclavicular node	.....	9/13/29, 3 high voltage treatments	....	9/21/29, 43.4 mc. in 15 gold seeds	235	..	930	1,165 in 1 mo.	Left axilla by 10.4 mc. in gold seeds; left infraclavicular space by 5.2 mc. in 2 gold seeds	Complete disappearance of all tumors in breast, axilla and infraclavicular space	

TABLE 13.—*Measured Tissue Dosage in the Irradiation of Primary Inoperable Carcinoma of the Breast—Continued*

Patient and Age	Size	Axillary Adenopathy	Cause of Inoperability	Operation	Roentgen Treatments	Radium Element Pack Treatments	Interstitial Treatments	Tissue Dosage in Breast, per Cent, Skin Erythema Doses: X-Rays	Radium Element Pack	Interstitial	Total	Other Irradiation	End-Results	Pathologic Histology
R. P. 37	6.5×6 cm.	+	Metastasis to bone and lungs	1/22/30, biopsy	1/23/30, 3 high voltage treatments	.....	1/22/30, 70 mc. in 25 gold seeds	145	..	1,130	1,275 in 10 days	Left axilla by 3 mc. in 2 gold seeds	Radiosensitive; complete disappearance of tumor	Biopsy before irradiation; small cell, highly malignant, infiltrating duct carcinoma
A. B. (2) 73	3.5×3.5 cm.	+	Hilar lymph nodes	10/5/29, biopsy	.....	.....	9/26/29, 33.65 mc. in 11 gold seeds	...	..	1,360	1,360	Right axilla by 13.7 mc. in gold seeds	Tumor replaced by scar; disappearance of axillary nodes	Biopsy ten days after irradiation; carcinoma in scar tissue
J. F. 48	3.5×3 cm.	0	Metastasis to lungs	9/28/29, biopsy	.....	9/11/29, 16,000 mg. hr. at 6 cm.	9/28/29, 32 mc. in 6 gold seeds	...	60	1,300	1,360 in 19 days	Left axilla by radium element pack plus 23.6 mc. in gold seeds	Only thickness of breast remains; local cure	Biopsy seventeen days after external irradiation; adenocarcinoma in walls of dilated ducts
A. F. 37	6.5×6.5×4.5 cm.	+	Inflammatory type	.....	11/11/29, 3 high voltage treatments	.....	11/27/29, 87.5 mc. in 47 gold seeds	60	..	1,400	1,460 in 22 days	Right axilla by x-rays plus 30.2 mc. in gold seeds	Regression; tumor quite small	
M. B. 58	Left, 4.5×4×3.5 cm.	+	Metastasis in lungs	11/6/29, local mastectomy of right breast	.....	.....	11/6/29, 60 mc. in 36 gold seeds in left breast	...	..	1,720	1,720	0	Tumor in left breast almost disappeared	Right breast amputated; bulky adenocarcinoma, grade 3, radiosensitive
C. K. 73	7.5×5.5×2 cm.	+	Bilateral axillary nodes	3/20/30, local mastectomy for radium ulcer	1/31/30, 3 low voltage treatments	.....	2/4/30, 119 mc. in 71 gold seeds	150	..	2,000	2,150 in 9 days	Right axilla by 30 mc. in 18 gold seeds	4/2/30, died; enormous radionecrotic ulcer on chest	Radium ulcer; in base were scattered foci of regressing carcinoma in scar tissue
M. C. 63	4.5×4×3.5 cm.	0	Cardiac disease	12/21/29, biopsy	.....	.....	12/21/30, 44 mc. in 20 gold seeds; 1/31/30, 32 mc. in 15 gold seeds	...	..	2,200	2,200	0	Tumor quite small, hard, fibrous, quiescent	Biopsy before irradiation; small cell duct carcinoma, grade 2; radioresistant; infiltrates fat and fibrous tissue
E. F. 62	3.5×3 cm.	+	Metastasis to lungs ?, diabetes	.....	6/17/29, 3 high voltage treatments	9/14/29, 16,000 mg. hr. at 6 cm.	11/1/29, 52 mc. in gold seeds	230	50	2,200	Cannot be added	Right axilla by x-rays	Tumor inactive, hard, fibrous lump, 2 cm.; metastases to lung stationary	

CASE 9.—*To illustrate the use of measured tissue doses of irradiation in the treatment of patients with inoperable mammary cancer.*

A. S., a colored widow, aged 58, applied to the Memorial Hospital on Aug. 28, 1929, complaining of a rapidly growing lump in the left breast. She had one child, now aged 26, whom she had nursed for one year without lactational difficulties. She had had four miscarriages. The menopause had occurred in 1916. In May, 1928, she first felt a lump in her left breast; this lump had increased rapidly in size during the six months prior to admission. On physical examination, the right breast was atrophied. The upper median segment of the left breast contained a hard, delimited tumor measuring 5.5 by 4 by 4 cm. There was definite fixation to the

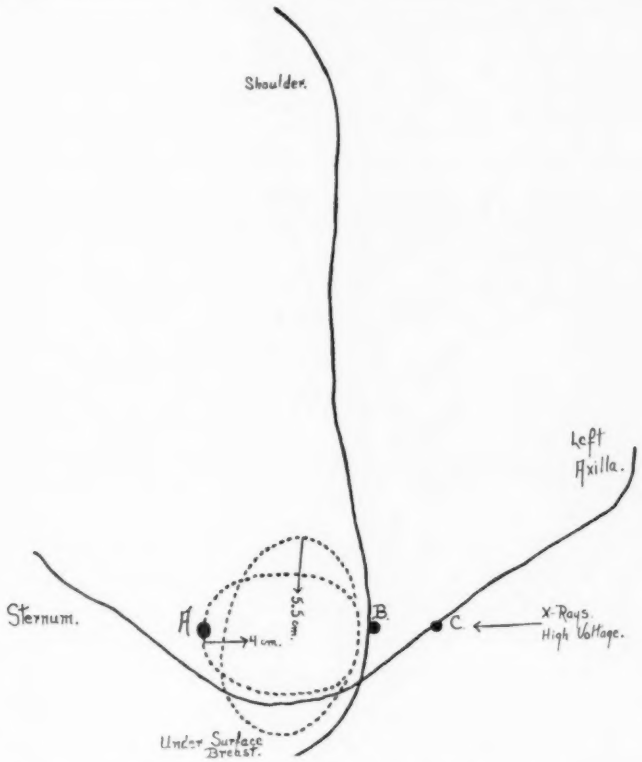

Fig. 28 (case 9).—Graphic representation of superimposed transverse and vertical contours of the left breast, illustrating the estimation of the depth of dosage by external irradiation.

superjacent skin, and the left nipple was contracted. The left axillae contained discrete large lymph nodes; there was one fixed hard nodule in the left infraclavicular space. A roentgenogram of the chest showed a very small nodular mass in the right hilus, which was interpreted as an early metastasis. The clinical diagnosis was primary inoperable carcinoma of the breast with metastases to the left axillary and infraclavicular nodes.

Immediate treatment was instituted, a high voltage roentgen cycle being applied to the left breast with drainage areas (from August 29 to September 17). This was followed on September 21 by the implantation of 15 gold radon seeds contain-

ing 43.43 millicuries in the mammary tumor, 4 gold seeds containing 10.4 millicuries in the left axilla and 2 gold seeds containing 5.2 millicuries in the infraclavicular node. The mammary tumor received a total of seven skin erythema doses in its depth. All palpable evidence of this mammary cancer had disappeared by October 21; the patient remained free from local recurrence in the irradiated area, but there has been some increase in the number and density of the peribronchial shadows.

Comment.—Primary inoperable mammary cancers may be treated by properly measured doses of irradiation in sufficient quantity to insure the disappearance of cancer in the breast and adjacent lymph nodes. This method constitutes the procedure of choice and is the only available measure for palliation and possible cure for inoperable carcinomas of the breast (fig. 28).

C. RECURRENT CARCINOMA OF THE BREAST

Few recurrent carcinomas of the breast are operable. During the last twelve years, 2,234 patients with carcinoma of the breast were treated at the Memorial Hospital; less than 50 of these patients had recurrent operable cancers. We define a recurrent operable mammary cancer as a single, freely movable tumor recurring in the operative field.

On the other hand, patients with recurrent inoperable carcinomas of the breast constitute the largest division or group admitted to the hospital, according to our plan of classification. The cases of recurrent inoperable carcinoma, of necessity belong entirely to the field of radiology, for radiation therapy offers the only hope of arresting or eliminating the disease or relieving many of its distressing symptoms. Frequently the recurrences together with possible distant metastases are too widespread for effective radium therapy. The presence of the operative scar and the multiplicity of the lesions militate against successful irradiation. When the breast has been amputated, a most valuable holder for interstitial irradiation is thereby lost. Recurrences in the wound or scar are in such close approximation to the thoracic wall that great caution must be exercised in the implantation of gold radon seeds, else the ribs will be injured by the radiations. The disappearance of the diffuse cutaneous recurrences of inflammatory carcinoma of the breast after roentgen treatment is striking. Diffuse recurrences are treated by roentgen rays rather than by the radium element pack for two reasons: the area of skin exposed can be larger, and the depth of the dose in the skin and subcutaneous tissues can be appreciably greater (table 3). In instances in which the recurrence is well localized, the radium tray, at 3 cm. focal distance, is applied for a dosage of from 3,000 to 3,500 millicurie hours. We have treated many patients with localized recurrent carcinomas by measured tissue doses of irradiation, using external irradiation followed by the implantation of gold radon seeds.

Recurrent carcinomas ulcerate quickly. The ulcer may spread widely, remaining superficial. We have had considerable success in treating these large superficial ulcers by unfiltered or very lightly filtered (from 1 to 2 mm. aluminum) roentgen rays, which stimulate rapid healing.

Late Changes in the Skin Following Irradiation.—When the low voltage type of roentgen treatment was given over a long time, especially in the primary inoperable cases, considerable atrophy of the skin and small telangiectases would sometimes appear two or three years later. In many cases these have increased in size and number, often covering the entire irradiated area; the extreme complication is ulceration and the supervention of squamous cell epithelioma. This necessitates wide excision of the leathery skin and subsequent skin-grafting. Our experience has led us to believe that small doses of irradiation repeated at intervals over a long time are far more likely to cause these changes than a single massive dose from which the skin recovers quickly with little resultant damage and no late complications. Our present method of administering all the radiation therapy in less than three weeks is not attended by significant late changes in the skin.

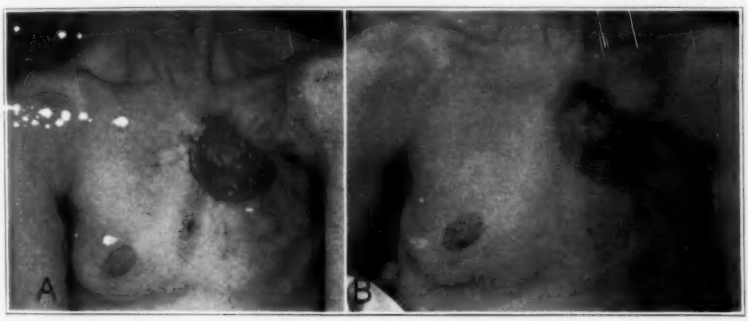

Fig. 29.—(*A*) Flat, superficial, ulcerated recurrent carcinoma of the left breast. (*B*) Clinical disappearance of recurrent tumor with epithelialization following two treatments by unfiltered roentgen rays.

Local Excision and Irradiation in Selected Cases of Mammary Carcinoma.—In general, we do not approve of the principle of local excision and irradiation of mammary cancer. In certain cases, however, this procedure has been carried out with success, notably whenever the original clinical diagnosis was mastitis or fibro-adenoma, and a frozen histologic section and microscopic diagnosis revealed carcinoma but the patient refused the complete operation; and whenever local wide excision of a suspicious lump in the breast was followed by the diagnosis of encapsulated papillary intraductular or papillary intracystic carcinoma, with no evidence of infiltration. Radical mastectomy is the procedure of choice, for though the carcinoma is of low grade malignancy and appears to have been excised completely, the possibility always remains that new carcinomas of similar structure may originate in other ducts or cysts within the same breast. In the event that the complete operation is not done and no regional metastases are known to exist, we have inserted

gold seeds widely through and in the fresh wound before suturing, thereby insuring accuracy of placement for the interstitial irradiation; sometimes, however, the healing of the wound is delayed. This is followed by heavy external irradiation (radium element pack or roentgen rays) over the breast and drainage areas.

SUMMARY

1. Preoperative external irradiation for mammary carcinoma is of value, as is proved by: (1) the occasional regression of tumors so treated; (2) the histologic changes produced, and (3) the better clinical end-results.

2. An efficient devitalizing dose cannot be delivered by external irradiation alone.

3. To deliver an efficient dose one must use interstititial irradiation.

4. The tissue dose delivered to the tumor should be measured and expressed in skin erythema units. This dose should be prescribed.

5. Tables prepared in the physical department enable the clinician to translate into terms of skin erythema units the tissue dose delivered, whether by external or interstitial irradiation.

6. The universal tissue dosage necessary to effect destruction of a radioresistant mammary cancer approximates twelve skin erythema doses.

7. The safest procedure is to treat all patients with mammary cancers with the same sufficient dose, because (1) radiosensitivity cannot always be determined before operation, and (2) the same tumor may contain radioresistant and radiosensitive areas.

8. Mammary cancers vary markedly with respect to radiosensitivity.

9. The mammary gland will tolerate safely an enormous dose of interstitial irradiation.

10. The possible menace of dissemination of the disease by the method of interstitial irradiation has been considered. We have not seen evidence of such a dissemination in this series. Preliminary external irradiation lessens this possibility.

11. All preoperative irradiation should be given within three weeks or less time.

12. Six weeks should elapse following interstitial irradiation before radical amputation is performed.

13. An interval of six weeks is necessary, because after this interval (1) the effects of irradiation are complete, (2) complete destruction of the tumor is accomplished and (3) wound healing is unimpaired.

14. Our present treatment for primary operable mammary cancer is external irradiation, then interstitial irradiation and finally radical amputation six weeks later.

15. The axilla is irradiated by (1) preoperative roentgen rays or radium element pack, followed by (2) interstitial gold-filtered radon distributed along the gland-bearing areas.

16. The pathologic changes produced in mammary cancer by external irradiation are mainly due to vascular effects. There are moderate hydropic swelling of the tumor cells, moderate atrophic degeneration, marked collagen swelling, productive arteritis with thrombosis and calcific deposits in the vessel walls and productive fibrosis.

17. The changes produced by interstitial irradiation are mainly direct effects on the tumor tissue, namely, ballooning degeneration, hydropic swelling, giant nuclei and atypical degenerative mitoses, a tendency toward squamous metaplasia followed by sloughing, hemorrhage, infiltration by fatty macrophages with ensuing extensive calcific deposits, often acute capillary necrosis with resultant tumor necrosis, squamous metaplasia of normal adjacent lobules in the breast, collagen swelling, productive fibrosis and late atrophy of the residual tumor.

NOTE.—In the continuation of this study, all new cases of primary operable carcinoma of the breast are divided into three categories for the purpose of evaluating the different methods of treatment, namely: (1) surgical intervention alone, (2) external and interstitial irradiation followed by surgical intervention and (3) irradiation alone. The patients for these groups are not selected, but are assigned in the order of their application to the clinic. Time will reveal the relative effectiveness of these procedures.

BIBLIOGRAPHY

Adair, F. E.: The Response of Various Types of Breast Cancer to Radiation, Radiology **13**:319, 1929.

Cutler, M.: Comparison of the Effects of Unfiltered and Filtered Radon Tubes Buried in Rabbit Muscle, Am. J. Roentgenol. **16**:535, 1926.

Dean, A. L.: Results of Skin Tests Made to Determine an Objective Dose for Radium Radiations, Am. J. Roentgenol. **10**:654, 1923.

Ewing, J.: Tissue Reactions to Radiation, Am. J. Roentgenol. **15**:93, 1926.

Factors Determining Radioresistance in Tumors, Radiology **14**:186, 1930.

Radiosensitivity, Radiology **13**:313, 1930.

Failla, G., and Quimby, E. H.: Economics of Dosimetry in Radiotherapy, Am. J. Roentgenol. **10**:944, 1923.

Keynes, G.: Radium Treatment of Primary Carcinoma of the Breast, Lancet **2**:108 (July 21) 1928.

The Treatment of Primary Carcinoma of the Breast with Radium, Acta radiol. **10**:393, 1929.

Radium Treatment of Carcinoma of the Breast, Lancet **1**:439 (March 1) 1930.

Lee, B. J.: Treatment of Recurrent Inoperable Carcinoma of the Breast by Radium and Roentgen-Ray, J. A. M. A. **79**:1574 (Nov. 4) 1922.

Results of the Treatment by Radiation of Primary Inoperable Carcinoma of the Breast, Ann. Surg. **74**:359, 1922.

Results and Technique in the Treatment of Carcinoma of the Breast by Radiation, Am. J. Roentgenol. **10**:62, 1923.

Radiation in the Treatment of Mammary Carcinoma, Canadian Practitioner **49**:141 (March) 1924.

The Therapeutic Value of Irradiation in the Treatment of Mammary Cancer, Ann. Surg. **88**:26 (July) 1928.

——and Cornell, N. W.: A Report of Eighty-Seven Primary Operable Cases of Carcinoma of the Breast, Tr. Am. S. A. **42**:275, 1924.

——and Herendeen, R. E.: The Treatment of Primary Inoperable Carcinoma of the Breast by Radiation, Radiology **2**:121 (March) 1924.

An Evaluation of Pre-Operative and Post-Operative Radiation in the Treatment of Mammary Carcinoma, Ann. Surg. **82**:404, 1925.

——and Pack, G. T.: Tissue Dosage Estimation in Mammary Cancer, Bull. Memorial Hosp., New York **1**:67, 1929.

——and Stubenbord, J. G.: A Clinical Index of Malignancy for Carcinoma of the Breast, Surg., Gynec. & Obst. **47**:812 (Dec.) 1928.

——and Tannenbaum, N. E.: Inflammatory Carcinoma of the Breast, Surg., Gynec. & Obst. **39**:580 (Nov.) 1924.

Recurrent Inoperable Carcinoma of the Breast, J. A. M. A. **86**:250 (Jan. 23) 1926.

Mandler, V.: Zur prophylaktischen Bestrahlung des Brustkrebses, Zentralbl. f. Chir. **56**:133, 1929.

Martin, H. E., and Quimby, E. H.: Calculations of Tissue Dosage in Radiation Therapy, Am. J. Roentgenol. **23**:173, 1930.

Quimby, E. H.: The Skin Erythema Dose with a Combination of Two Types of Radiation, Am. J. Roentgenol. **17**:621, 1927.

The Intensity of Radiation in the Vicinity of Filtered Radon Implants, Radiology **10**:365, 1928.

——and Martin, H. E.: A Basis for Dosage Determination in Interstitial Irradiation, Am. J. Roentgenol. **21**:240, 1929.

——and Pack, G. T.: The Skin Erythema for Combinations of Gamma and Roentgen Rays, Radiology **13**:306 (Oct.) 1929; Further Studies on the Skin Erythema with Combinations of Two Types of Radiation, ibid. **15**:30 (July) 1930.

Treves, N., and Pack, G. T.: An Unusually Radiosensitive Breast Tumor, Bull. Memorial Hosp., New York **2**:55, 1930.

DISEASES OF THE LARGE INTESTINE*

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Diseases and abnormalities of the large intestine are far too numerous to be described in one paper; I shall discuss, therefore, only the more common conditions that may be encountered in the routine examination of the gastro-intestinal tract.

The normal contour and position of the colon, as well as many of the abnormal positions that it may assume, are familiar to all physicians. It may not be so well known, however, that a transverse colon that crosses the upper part of the abdomen is more or less rare. In the majority of cases, one finds that the colon falls well below the umbilicus, and it is not unusual to find a transverse colon with its midpoint below the urinary bladder. In many cases the rotation of the colon is incomplete; frequently the embryonic stage is not fully resolved. The normal sigmoid flexure is generally from 16 to 17 inches long (40.6 to 43.1 cm.), but this length may vary, a redundant sigmoid sometimes being several feet in length. Doubtless some cases of obstipation are due entirely to this redundancy. The dilated colon, also, is often a source of difficulty. At the present time, extensive work is being done in an effort to prove that, in some cases at least, colonic stasis is directly responsible for arthritis, stasis being apt to occur, of course, when the colon is dilated, spastic or redundant. The intestinal activity is accelerated in the presence of hyperthyroidism, and diarrhea may be expected to occur; conversely, hypothyroidism is held responsible for hypomotility of the intestines, with its accompanying symptoms of constipation and toxemia.

SPASTIC COLITIS

The etiology of spastic colitis has not been ascertained, although many theories have been advanced to account for the syndrome designated by this name; some writers even argue that it is not a definite condition, and many competent clinicians ignore its existence completely. It is my belief that spasticity of the colon is a real entity and one that can be definitely demonstrated. In the majority of cases, the condition does not become serious, although at times it causes alarming symptoms which may be readily misinterpreted. This misinterpretation occurred, in fact, in two cases that recently came under my observation.

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* From the Cleveland Clinic.

In one of these cases the roentgenogram showed a constant filling defect in the sigmoid flexure. At operation, the only finding was spasticity in the area of the roentgenographic deformity. In the other

Fig. 1.—Roentgenogram illustrating a case of stone in the appendix of a child. This was a retrocecal appendix that had ruptured. The arrow points to the stone.

Fig. 2.—Megacolon in a child. Note that the colon almost entirely fills the abdomen.

case the same principle was illustrated, although the spastic area was not in the colon. All the cardinal symptoms of complete intestinal obstruction were present in the latter case, and consequently an opera-

tion was performed. The patient died on the operating table, and at autopsy a spastic area in the jejunum was disclosed. Had a test been made with atropine or some other antispasmodic, doubtless an operation would not have been performed and the patient would still be alive.

Spastic colitis is a functional condition that may give rise to numerous symptoms, the most common of which are constipation, flatulence, abdominal malaise and pain (either localized or general). If the spasticity persists, it may lead to an inflammatory change with

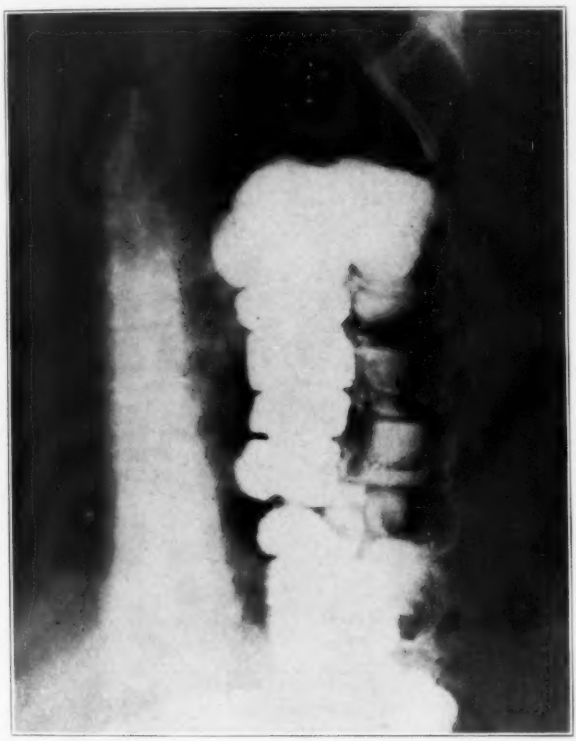

Fig. 3.—Roentgenogram showing a portion of the colon herniated high into the left pulmonic field.

its accompanying symptoms. Since constipation is the most constant symptom, it is surprising to learn that often there is marked colonic hypermotility, the head of the barium meal reaching the rectum in a few hours. This is not difficult to understand, however, in view of the mechanism that causes spastic colitis. According to Gauss,[1] several theories have been advanced to explain hypertonicity. Among these theories are those of an unstable nervous system, a submerged

1. Gauss, H.: The Spastic Colon, Ann. Int. Med. **3**:1128, 1930.

fear complex acquired in early life and an inherited spasmophilic tendency. "The direct etiologic factor is an open problem today. Nevertheless, it has been observed that usually the patient with a spastic colon is a neurotic individual given to introspection, and that the hypertonicity of the colon is a local manifestation of a general spasmophilic tendency." Spasticity, no doubt, is the underlying cause, this being due to a variable degree of reflex contraction of the smooth muscle fibers.

ULCERATIVE COLITIS

It is probable that ulcerative colitis is caused by an infection that has been superimposed on tissues the resistance of which has been

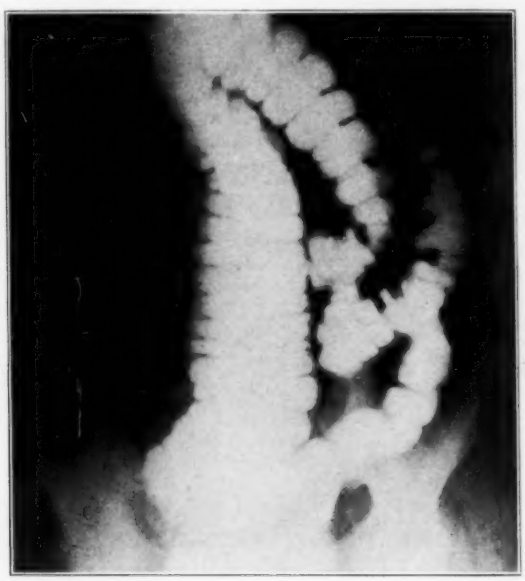

Fig. 4.—Roentgenogram showing an abnormal position of the proximal colon. Scarcely any of the colon is seen to the right of the midline. The cecum and appendix are low in the pelvis.

lowered as the result of a predisposing condition, such as long-standing catarrhal inflammation of the bowel or severe spasticity of the colon. The ulcerations vary greatly in size, some being only as large as a pinhead while others completely surround the lumen of the colon. Some ulcerations may be very superficial, becoming completely healed in a few days, while others may extend to the muscular coat or may even penetrate the wall of the colon and involve the peritoneum.

The disease is apt to be sudden in its onset, with lancinating pains over the course of the colon, accompanied by griping and frequent bowel movements. There are severe constitutional disturbances, and

in those cases in which the disease is progressive, despite treatment, the resulting mental condition parallels the effect of the toxemia on the nervous system. These attacks occur in cycles, and between them the patient has complete comfort. After a few attacks, mucus, pus and blood are passed, and in severe cases the condition of the patient is distressing.

Ulcerative colitis may be confused with dysentery, typhoid fever or a malignant condition. It presents many of the characteristics of the later stages of bacillary dysentery, but is not so fulminating in its onset and does not produce profound toxemia, and the fever seldom is as high as in the former condition. The final differentiation, however, depends on the results of stool cultures and agglutination tests. Amebic dysentery is more gradual in its onset; it presents stools con-

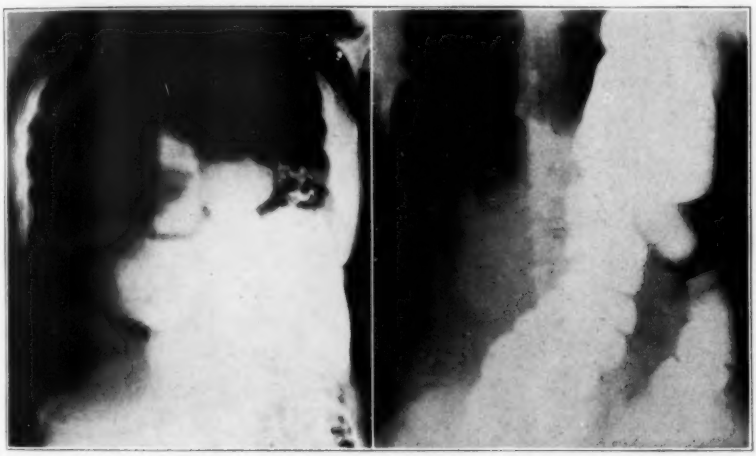

Fig. 5.—Roentgenograms showing hernia of the diaphragm on the left.

taining amebae and gray, blood-stained or yellow mucus, and the condition of the patient is improved after three or four days of treatment with emetine hydrochloride. In this country, chronic bacillary dysentery is less common than is chronic ulcerative colitis, and its diagnosis is made by agglutination tests. Examination with the sigmoidoscope may reveal tumors or ulcers in the rectum and permit the obtaining from them of mucus, a slough or a scraping for examination or culture. A roentgenogram may be helpful in the recognition of colitis by revealing the presence of spasm or areas of ulceration.

Typhoid fever may be differentiated from ulcerative colitis by a history of exposure to a source of infection, followed in two or three weeks by an insidious onset, and at the end of another week by the development of rose spots and enlargement of the spleen. The temperature curve in typhoid fever usually is characteristic, and there are

progressive leukopenia and lymphocytosis. Blood cultures may give positive results as early as the second day, and the Widal reaction is positive after the tenth day.

Cancer develops much more slowly than ulcerative colitis, and pain and griping are rarely seen early in malignant disease. Constipation is one of the earliest symptoms of carcinoma, as is the case in colitis, but

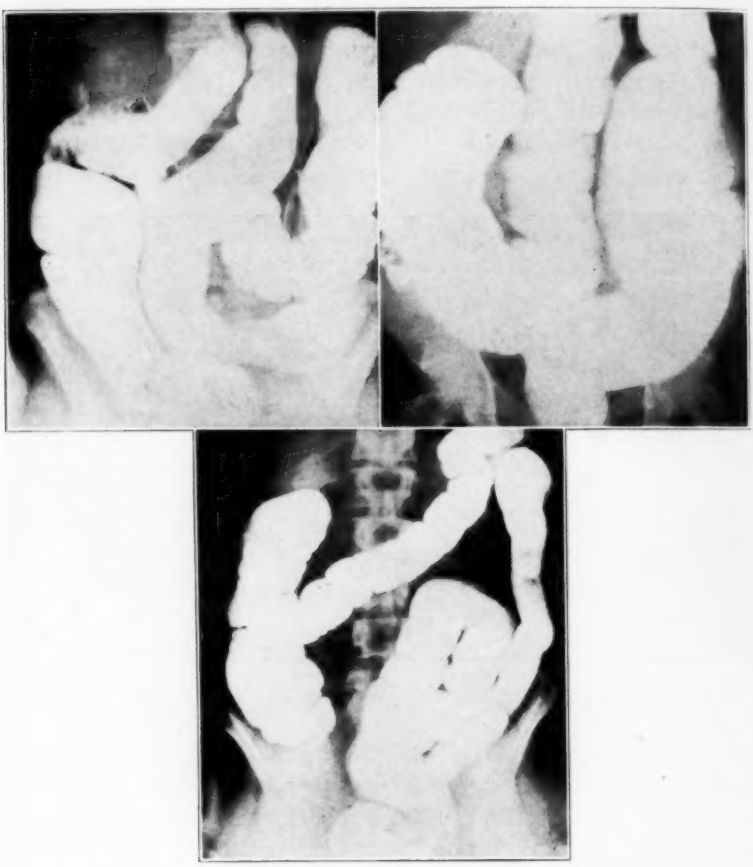

Fig. 6.—Roentgenograms showing varying degrees of redundant sigmoid.

in a case of carcinoma the patient is comfortable after the bowels have moved, except in the late stages of the disease, while in colitis a bowel movement fails to give relief.

PERICOLITIS

The manifestations of pericolitis vary with the duration of the condition, the type and virulence of the infecting organism and the length of intestine involved. The chief symptoms are constipation, alternating

with occasional diarrhea, constitutional disorders resulting from absorption, localized abdominal soreness or pain on pressure, a palpable abdominal mass, which may readily be mistaken for a tumor, and mucus or blood in the stools. Mild and sometimes alarming symptoms of intestinal obstruction may be present, depending on the degree of nar-

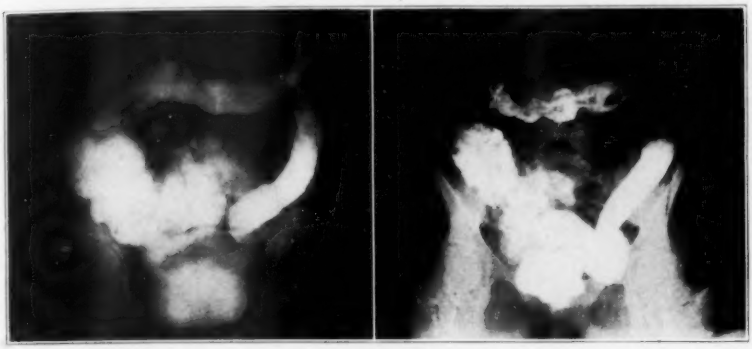

Fig. 7.—Two cases of chronic ulcerative colitis. Note the loss of tone in the colon.

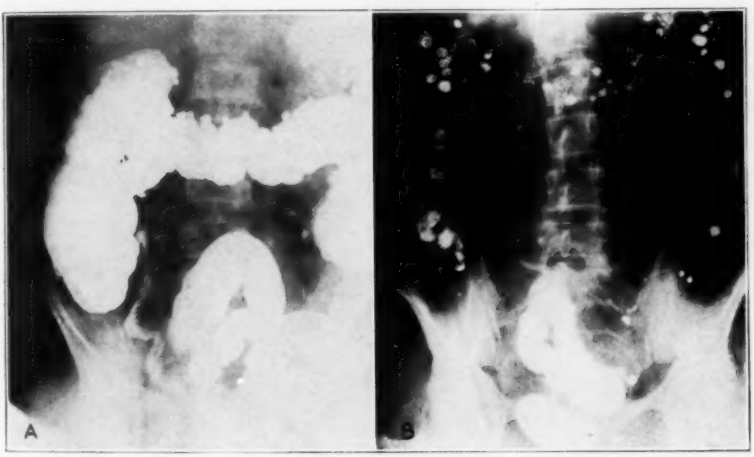

Fig. 8.—*A,* a case of diverticulosis. Note the diverticula along the entire course of the colon. *B,* roentgenogram of a typical colon twenty-four hours after the administration of barium, showing many diverticula.

rowing of the lumen of that portion of the colon involved. In cases in which the temperature is high, an abscess may be suspected.

In obscure cases it is necessary to differentiate between this condition and appendicitis, diverticulitis and cholecystitis. Fluoroscopic examination and roentgenograms following a barium sulphate enema will often aid in making the differential diagnosis, although in diver-

ticulitis the enema is not so important as the twenty-four hour barium examination, since barium sulphate when given by mouth is so much more certain to fill a diverticulum than when given by enema.

APPENDICITIS

I do not mean to imply that all cases of appendicitis can be diagnosed by roentgenograms, but many cases cannot be diagnosed pre-

Fig. 9.—*A*, roentgenogram of sigmoid extending to right lower quadrant. Note several small diverticula in the sigmoid. *B*, diverticulosis of the sigmoid. Note the long loop of sigmoid with evidence of pressure from an extrinsic mass. *C*, roentgenogram showing almost complete obstruction in the sigmoid due to a large inflammatory mass in the area designated by the arrow. The presence of several small diverticula proximal to the lesion is evidence in flavor of a nonmalignant tumor.

operatively by any other method. Acute appendicitis is not a problem for the roentgenologist, but one that should be handled promptly by

the surgeon. The cases in which roentgenographic study is of value are those in which there is a history of vague abdominal uneasiness or distress, with a digestion that is not up to par. In many instances suspected cholecystitis can be ruled out by the roentgenographic demonstration of incomplete rotation of the colon which leaves the cecum and

Fig. 10.—*A,* roentgenogram showing the cecum lying high in the right upper quadrant. It is in such cases as this that a diagnosis of appendicitis is difficult. *B,* a similar case. The arrow points to the tip of the appendix lying high under the liver. *C,* roentgenogram showing the cecum lying in the midline. *D,* roentgenogram showing the cecum lying far to the left. Should appendicitis develop in this case, it would be difficult to diagnose. Symptoms would be referred to the lower left quadrant.

appendix in the region of the gallbladder. Often also it is possible to demonstrate the presence of an elongated retrocecal appendix with the

tip high up under the hepatic flexure, a finding that is of value in the differential diagnosis and of assistance to the surgeon in planning his incision. The presence of stones in the appendix also can be demonstrated roentgenographically, as well as adhesions that prevent the free movement characteristic of the normal appendix. In other types of appendiceal disease an irregular filling can be demonstrated that corresponds to definite localized tenderness. It is not often that the appendix is found in the classic McBurney position, but it can be localized accu-

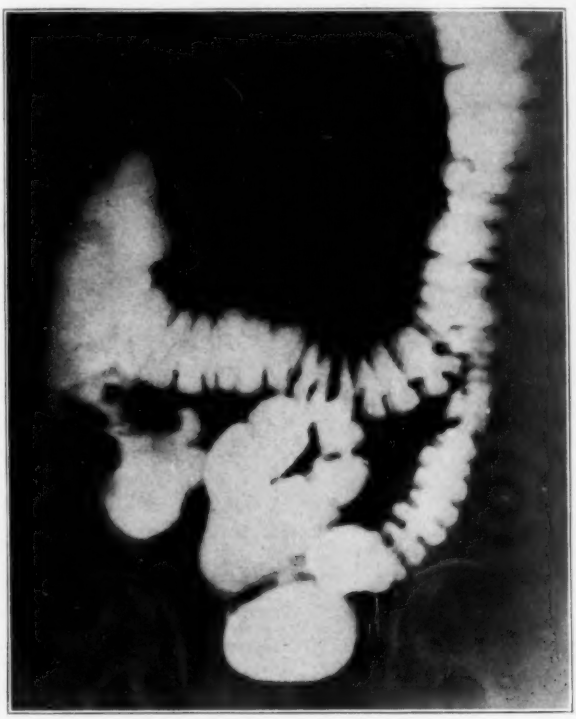

Fig. 11.—Roentgenogram showing a large filling defect in the first portion of the ascending colon due to carcinoma.

rately with x-rays, while pressure will determine the presence or absence of tenderness. Delayed emptying of the appendix (from twenty-four to seventy-two hours after the head of the colon has emptied) is thought by some authorities to be evidence of chronic appendicitis.

FOREIGN BODIES

The presence of foreign bodies can be demonstrated roentgenographically only when they are of opaque material. Serial roentgenograms and fluoroscopic examinations are essential in order to follow

the progress of the foreign body through the intestinal tract and to make sure that it has not lodged at some vulnerable point.

TUBERCULOSIS

Tuberculosis of the colon and rectum may be either primary or secondary. In a review of 100 cases, Gant [2] found that the infection was secondary in 75 per cent, and that in the majority of these the foci were located in the lungs, larynx or pharynx. Primary tuberculosis of the colon usually develops in the cecum or at the anus, while secondary lesions may be found anywhere in the intestinal tract, although they, too, are found most frequently in the cecum and rectum. Many factors contribute to produce this result, such as the greater speed of the intes-

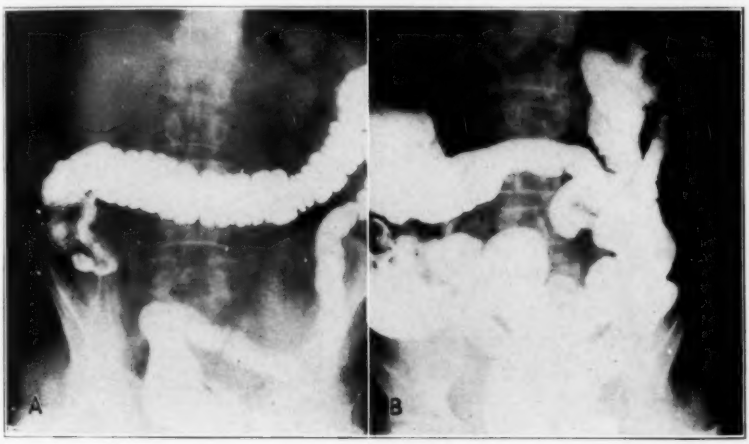

Fig. 12.—*A*, roentgenogram showing a filling defect in the cecum due to carcinoma. *B*, roentgenogram showing a filling defect in the ascending colon due to a large carcinoma.

tinal content through the small bowel, which does not permit the bacilli to find lodgment there; attenuation of the bacilli by the gastric juices, their virulence not being recovered until the cecum or colon is reached; the alkaline reaction of the feces after the ileocecal region is attained, which provides a more propitious environment for the bacilli; the formation of hardened masses of feces in the cecum, which traumatize the mucosa and produce conditions favorable to infection, and the abundant lymphatic distribution in the ileocecal region, which favors the development of tuberculosis.

Several types of tuberculosis are found in the colon, the most common of which are the hyperplastic, ulcerative and miliary.

2. Gant, S. G.: Diseases of the Rectum, Anus and Colon, Philadelphia, W. B. Saunders Company, 1923, vol. 3, p. 43.

Hyperplastic tuberculosis occurs in both children and adults, most frequently in the third decade. It may be primary or it may be secondary to a focus higher up in the intestines or in some other organ. It produces a slow-growing tumor which at times is quiescent for two or three years before it attains sufficient size to occlude the lumen of the intestine and produce symptoms of obstruction. These tumors usually feel smooth when palpated, but examination of a gross section reveals a very irregular, hard and brittle type of tissue. Usually they are fixed, but they may be slightly movable. The rigidity of the terminal ileal segment is a characteristic roentgenographic observation.

In the ulcerative type of tuberculosis, the ulcers may be superficial or deep. Superficial ulceration may heal promptly, but deep ulceration progresses rapidly and is almost impossible to control. The mixed

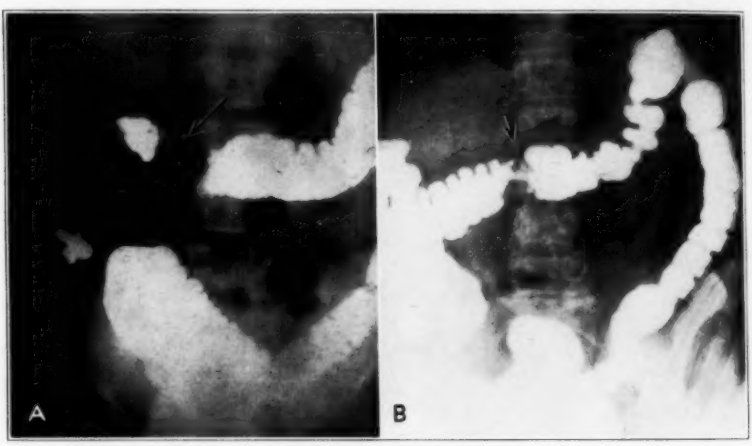

Fig. 13.—*A*, the arrow points to a deformity in the transverse colon due to carcinoma. *B*, a similar case, but less obstruction is present. However, note the beginning dilatation of the colon proximal to the obstructing area.

infection that must follow soon causes toxemia, imperfect digestion, constitutional manifestations, persistent diarrhea and extensive destruction of the mucosa and deeper bowel coverings. Hemorrhage, peritonitis, abscess, adhesions and other serious complications may be encountered, and if surgical intervention were instituted, a generalized miliary tuberculosis of all the abdominal viscera might be found.

The prognosis of intestinal miliary tuberculosis is unfavorable because it is secondary to a well established process elsewhere, and the patient is debilitated and unable to withstand the ravages of the fast-spreading tuberculous process.

DIVERTICULA

A diverticulum is a non-neoplastic outpouching of intestine, having a lumen that connects with the bowel or that formerly connected with it.

Diverticula may be congenital (true) or acquired (false), the latter form appearing more often between the ages of 40 and 60 years, and about twice as frequently in men as in women. Diverticula may develop at any point along the course of the colon, but are found most commonly in the sigmoid flexure, the descending colon, the cecum and the transverse colon. The hepatic flexure also is frequently involved, and diverticulitis at this point is at times most difficult to differentiate.

Diverticula may be single or multiple, large or small, smooth or irregular. The sacs may be quiescent for many years and then suddenly become obstructed, resulting in acute inflammation. Symptoms may then become severe and lead to the belief that appendicitis, peritonitis, intestinal obstruction, a new growth, or an abscess is present. Definite

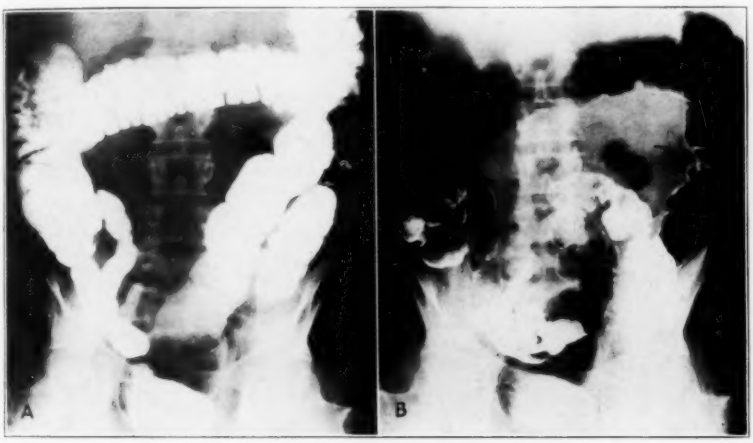

Fig. 14.—*A*, a filling defect as seen fluoroscopically in the lower descending colon. The loop of the sigmoid obscures the deformed area. *B*, the same case after air has been injected into the colon. The arrow points to a filling defect due to carcinoma.

proof that many diverticula never produce symptoms is presented by the frequent finding of such pouches during the course of routine gastro-intestinal examinations and at autopsy.

Diverticulitis may be acute or chronic, more often the latter. Because of the size, form, consistency and macroscopic appearance of the tumor, a diverticulum often is mistaken for carcinoma. Doubtless many of the supposed carcinomas that have been reported cured by operation have in reality been merely inflammatory masses caused by diverticulitis. It may be that these diverticula are a predisposing cause of carcinoma, but to determine this definitely would require extensive research.

After the onset of inflammation in a severe case of diverticulitis, there will be localized tenderness, intense cramps and constipation with a sensation of blocking. When the lumen is almost occluded there are a marked formation of gas, severe pain, muscular rigidity, nausea and vomiting, an increased temperature and pulse rate and mucus, pus and blood in the stools. If the process progresses to the point of rupture, the usual symptoms of spreading peritonitis are present. If an abscess forms, there is continued localized pain and swelling until it has ruptured into the intestine or peritoneal cavity or has been drained.

Given a history of chronic left-sided inflammation, with periodic exacerbations and an absence of cachexia and loss of weight, a diag-

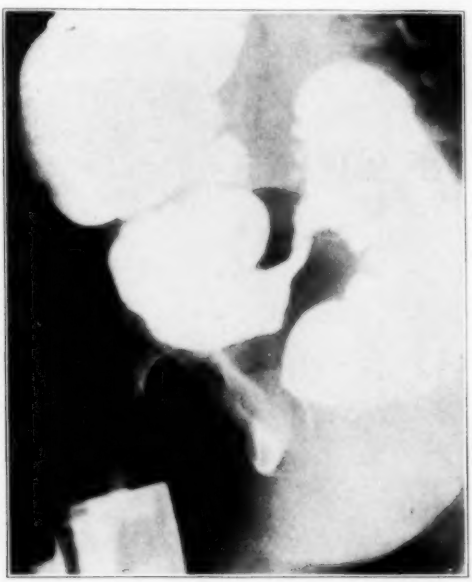

Fig. 15.—Roentgenogram showing carcinoma of the sigmoid. This could not be seen with the patient lying flat. The film was exposed with the right side of the patient uppermost. The sigmoid is a frequent location for carcinoma. The coils of the lower sigmoid and rectum overshadow these growths.

nosis of diverticulitis usually is justified. Proctoscopic examination may reveal a small opening from which pus is draining, and pus in the bowel is suggestive of diverticulitis.

If the patient's condition is extremely grave, it is not advisable to subject him to a roentgenographic examination. Cases have been diagnosed, however, in which the obstruction was almost complete, a barium sulphate enema showing the filling defect. It is often impossible to make the differentiation on the basis of the roentgen examination alone, but the small cavitation that is present in carcinoma is rarely seen in

diverticulitis. The deformity, of course, is due to narrowing of the lumen of the colon, but in diverticulitis there is, as a rule, no break in the mucosa and the rugae can be seen in the deformity.

CARCINOMA

Unfortunately, early carcinoma of the colon is difficult to diagnose roentgenographically, as a filling defect does not develop until the late stages of the disease. It is impossible to see the early ulcerations, and a mass must be present that will displace a portion of the column of barium sulphate in the colon before a diagnosis can be made. After the growth has become large enough to produce partial obstruction, dilatation of the colon proximal to the lesion will be noticed. In many instances carcinoma of any portion of the colon may be overlooked if redundancies cover up the lesion. A fluoroscopic examination should be made from all angles, therefore, in an effort to throw these redundant loops out of the field of vision and pick up some small filling defect on either the anterior or the posterior wall of the intestine. Patients suffering from early carcinoma of the colon, however, seldom present themselves for roentgenographic examination.

Fully developed cancer of the colon usually produces fairly typical symptoms: alternating constipation and diarrhea, distention of the colon, tenderness, localized abdominal pain, attacks of offensive discharge containing mucus, blood, pus and possibly tissue fragments, loss of weight, cachexia, visible peristalsis and a filling defect, with evidence of dilatation of the colon proximal to this defect. It is often difficult to pass any of the opaque medium through the area of partial obstruction when the barium meal is given by enema, though a small amount may pass the obstruction when the barium meal is given by mouth. Atropine and other antispasmodics offer little assistance in the passage of the enema through the deformed area. When cecal carcinoma is suspected, a delay in ileal emptying is a significant sign. A proctoscopic examination should always be made before a barium sulphate enema is administered, in order to detect any evidence of the disease that may be visible in the rectum or lower bowel. Barium sulphate should not be given before this examination is complete, as it coats the bowel and obscures any evidence of disease that may be present.

OPERATIONS ON THE SUPERIOR POLE OF THE THYROID*

C. A. ROEDER, M.D.
OMAHA

The most successful operations on the goitrous or toxic thyroid comprise the preservation of parathyroid, laryngeal and tracheal function and the removal of enough glandular tissue to allow thyroid function to be controlled by the patient's physiologic reactions or by the administration of desiccated thyroid extract. The accidental injuries to the recurrent laryngeal nerves and parathyroid have encouraged most of the attention of surgeons to the middle and lower portions of the gland.

From observations of my own series of over 1,800 resections of all types of goiters and of many more operated on by other surgeons, I have witnessed an undesirably high percentage of changes in the tone of the voice, i. e., a lower pitch with a decreased range and huskiness, with or without a partial loss and lasting for a varying length of time. Changes in the voice and moderate obstructions to inspiration are generally of short duration and due, in nearly all instances, to a congestion of the mucous membranes of the larynx and trachea, postoperative immobility of the larynx, loss of vocal cord tension and temporary injuries to the superior and inferior laryngeal nerves producing incomplete abductor and adductor vocal cord immobility. During all voice changes, and when particularly prolonged, a hysteroid background must be kept under consideration.

Surgical trauma during resections of goitrous thyroids is often not followed by a corresponding degree of aphonia or laryngeal dyspnea. Surgeons frequently see examples of adductor or abductor vocal cord paralysis in which they feel positive that the inferior laryngeal nerve had not been traumatized in any manner. They have also expected a loss of voice following the removal of deeply lying and adherent adenomas, operations which could hardly have failed to injure the inferior laryngeal nerves, and they have been greatly surprised to hear the patient talk almost as well as ever. These two differing experiences suggest that the innervation of the larynx is at times irregular and not as well understood as one desires. Adductor paralysis results in a loss

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* From the Department of Surgery, University of Nebraska.

* Read in part before a meeting of the state societies of Wyoming, Montana and Idaho, Yellowstone Park, Aug. 12, 1928.

of voice, while abductor paralysis results in laryngeal dyspnea. Both conditions are generally assumed to be due to injury to the inferior laryngeal nerves. Loss of vocal cord tension results in a husky and lower tone of voice, which is often due to paralysis of the cricothyroid muscles innervated by the superior laryngeal nerve. Postoperative changes in the voice, obstructive dyspnea and tetany have turned almost the entire technical attention of surgeons to the middle and lower portions of goitrous thyroids. The object of this paper is to demonstrate that the removal of the superior pole of the thyroid, although easier, may be followed by at least as many complications as resections of any other portion of the gland. The parathyroids are often found lower than the superior pole and are here of less surgical importance. The only parathyroids present, however, may be attached to the superior pole.

THE PRETRACHEAL FASCIA

The thyroid gland is covered anteriorly and laterally by the so-called capsule which is derived from the middle or pretracheal layer of cervical fascia, and has been described by the majority of all authors as enclosing the entire gland. Only by embryologic studies, however, can this be definitely determined. Whether the gland reaches its usual position before the development of the pretracheal fascia or whether the fascia develops before the gland has fully descended are two questions of importance. Both, however, preclude the thought that this fascia surrounds the posterior surface of the thyroid. The dissections of Fowler and Hanson,[1] comprising 200 glands, did not in one instance show this layer of fascia enclosing the posterior and inner surfaces of each lobe. Their findings correspond with those in many of my own surgical dissections, which showed a reflection of this fascia away from the posterolateral border of the gland to encircle the esophagus. Testut [2] described and illustrated this fascia as just stated. In other words, it is more reasonable to state that the thyroid does not possess a capsule but lies behind the pretracheal fascia, which continues its course the same as if the gland were not present. There is a thin closely adherent capsule developed from interparenchymatous tissue which is of non-surgical use or importance.

The pretracheal fascia apparently folds over the anterior, external and internal surfaces of the superior pole, surrounding it more than any other portion of the thyroid, and binds this portion of the gland to the external lateral surfaces of the laryngeal cartilages and muscles. At the superior pole, therefore, it acts as a three-quarter sheath, and as it continues upward to be attached to the hyoid bone, it more or less

1. Fowler and Hanson: Surg., Gynec. & Obst. **49**:59 (Oct.) 1929.

2. Testut: Traité d'anatomie humaine, ed. 7, Paris, Gaston Doin, vol. 1, p. 776.

encapsulates the superior thyroid vessels and contains, within a separate compartment on its internal surface, the external branch of the superior laryngeal nerve. As the fascia lies opposite the thyrohyoid membrane, it is attached for several centimeters to the internal branch of the superior laryngeal nerve just before it passes beneath the medial upper border of the inferior constrictor muscle of the pharynx, which border often lies lower than the upper extremity of even the normal superior thyroid pole. Forcibly pulling this fascia downward by traction on the superior pole, with or without high mass ligations, may injure the internal as well as the external branch of the superior laryngeal nerve (fig. 2).

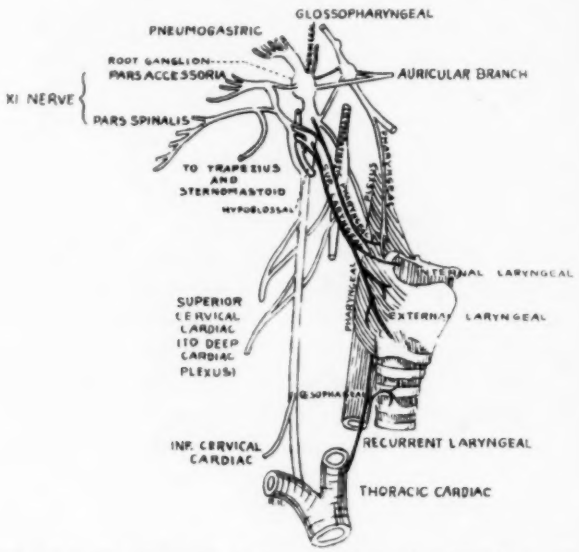

Fig. 1.—Nerve trunks that may be involved following ligations and the removal of the superior thyroid pole, resulting in: (1) compete or partial loss of the voice; (2) laryngeal obstructive dyspnea; (3) aspiration of ingested fluids into the bronchi; (4) loss of sensation to the mucosa of the upper sphincteric larynx; (5) the thyromandibular reflex; (6) the vagopinna reflex; (7) paralysis of the soft palate, and (8) referred pain throughout the somatic distribution of the first four cervical nerves.

The upper extremity of the superior pole of the thyroid, in a normal condition, usually lies opposite the upper portion of the lateral surface of the thyroid cartilage. Not infrequently, and particularly when hypertrophied, it lies opposed to the thyrohyoid membrane (fig. 2), and I have found enlarged poles lying against and even above the hyoid bone. In short-necked persons any sized gland may lie relatively much higher. Most anatomic textbooks describe the upper pole of a normal gland in a lower position than it is generally found in the living sub-

ject, owing, perhaps, to cadaveric contraction. The upper extremity of the pole generally lies higher than the gland's first point of contact with the superior thyroid artery, which is on its anterior surface. In endeavoring to ligate the vessels before they reach the upper level of the superior pole of an enlarged gland with a high superior pole, the ligature or clamp must therefore lie close to or opposite the thyrohyoid membrane. In such ligations, particularly with the high lying or goitrous superior pole, the internal as well as the external branches of the superior laryngeal nerve may be involved (fig. 2).

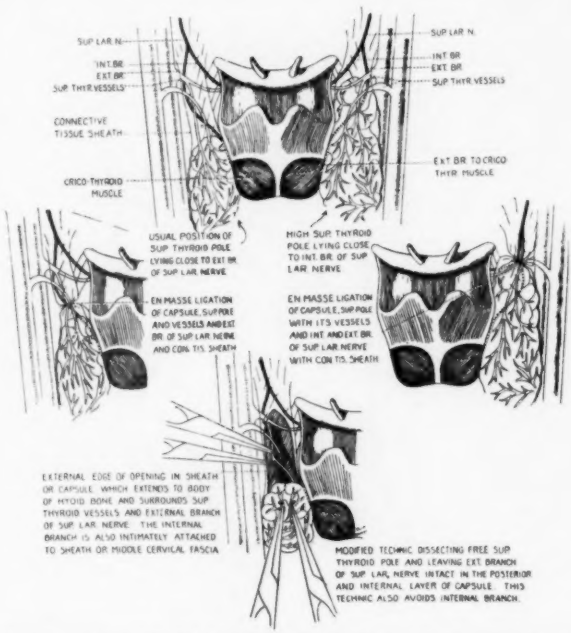
SUP LAR N.
INT BR
EXT BR
SUP THYR VESSELS
CONNECTIVE TISSUE SHEATH
CRICO-THYROID MUSCLE
SUP LAR N.
INT BR
EXT BR
SUP THYR VESSELS
EXT BR TO CRICO THYR MUSCLE
USUAL POSITION OF SUP THYROID POLE LYING CLOSE TO EXT BR OF SUP LAR NERVE
EN MASSE LIGATION OF CAPSULE, SUP POLE AND VESSELS AND EXT BR OF SUP LAR NERVE AND CONN TIS SHEATH
HIGH SUP THYROID POLE LYING CLOSE TO INT BR OF SUP LAR NERVE
EN MASSE LIGATION OF CAPSULE, SUP POLE WITH ITS VESSELS AND INT AND EXT BR OF SUP LAR NERVE WITH CONN TIS SHEATH
EXTERNAL EDGE OF OPENING IN SHEATH OR CAPSULE WHICH EXTENDS TO BODY OF HYOID BONE AND SURROUNDS SUP THYROID VESSELS AND EXTERNAL BRANCH OF SUP LAR NERVE THE INTERNAL BRANCH IS ALSO INTIMATELY ATTACHED TO SHEATH OR MIDDLE CERVICAL FASCIA
MODIFIED TECHNIC DISSECTING FREE SUP THYROID POLE AND LEAVING EXT BRANCH OF SUP LAR NERVE INTACT IN THE POSTERIOR AND INTERNAL LAYER OF CAPSULE THIS TECHNIC ALSO AVOIDS INTERNAL BRANCH.

Fig. 2.—Upper, moderately high and high positions of the superior poles. Right, ligature involving vessels of the superior pole and the external branch of the superior laryngeal nerve. Left, ligature involving vessels of the superior pole and both external and internal branches of the superior laryngeal nerve. Lower, new technic which dissects the superior pole from behind the thyroid sheath, leaving both branches of the superior laryngeal nerve intact.

Not infrequently, there is a posterior branch of the superior thyroid artery which lies along the posterior border of the superior pole, and often within a centimeter of the upper extremity of the inferior laryngeal nerve just before it passes beneath the lower borders of the inferior constricting muscle of the pharynx and the thyroid cartilage. In clamping or ligating the posterior branch of the superior thyroid artery near the inferior border of the thyroid cartilage, particularly while pulling the pole downward and across the trachea, the recurrent laryngeal nerve

may be injured (fig. 4). Occasionally, a high lying inferior thyroid artery approaches the gland along the lateral surface of the superior pole, within a centimeter or two of the inferior laryngeal nerve, which may be included during an attempt to ligate the vessel in this vicinity (Fig. 4). It is therefore possible to injure both branches of the superior laryngeal nerve and the upper portion of the inferior laryngeal nerve in the production of hemostasis of the superior pole.

Most anatomic textbooks infer that the superior laryngeal nerve supplies sensation to the mucosa of the larynx and supplies motor

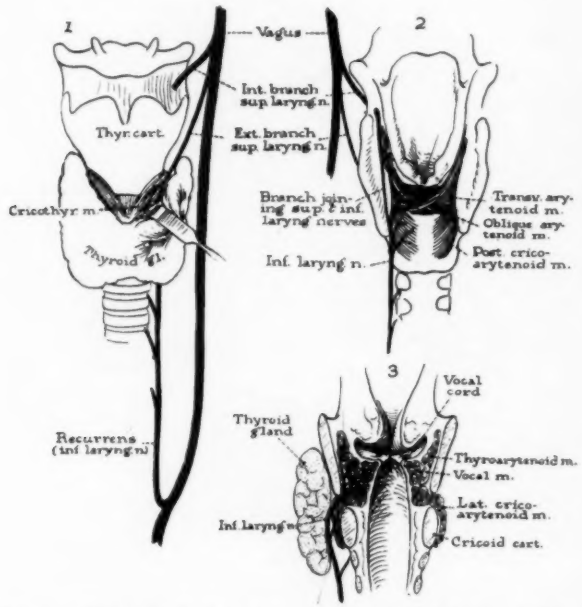

Fig. 3.—Laryngeal branches of the vagus nerve, which prove the tenth cranial nerve to be a mixture of voluntary and involuntary motor and sensory, as well as sympathetic and parasympathetic, fibers. Note in *2* a branch from the superior laryngeal supplying motor fibers to the adductor or interarytenoid muscle.

activity to only one muscle, the cricothyroid. The recent anatomic contributions by Berlin and Lahey, [3] Fowler and Hanson,[1] Dilworth,[4] New,[5] Mullin [6] and Nordland [7] not only are instructive but further prove that the interarytenoid muscles, adductors of the posterior ends of the vocal cords, frequently receive innervation from the internal

3. Berlin and Lehey: Surg., Gynec. & Obst. **49**:102 (Oct.) 1929.
4. Dilworth, T. F. M.: J. Anat. **56**:48, 1921-1922.
5. New, G. B.: Ann. Clin. Med. **1**:262, 1923.
6. Mullin, W. D.: Ann. Otol. Rhin. & Laryng. **37**:627, 1928.
7. Nordland, Martin: Surg., Gynec. & Obst. **51**:449 (Oct.) 1930.

branch of the superior laryngeal nerve. Vegus [8] also stated that the interarytenoid muscles in some instances receive branches from the internal branch of the superior layngeal nerve, that the recurrent laryngeal nerve subserves sensation up to the level of the vocal cords, and that above this, sensation is from the internal branch of the superior laryngeal nerve.

I found in one instance, during the dissection of three larynges, that a twig from the internal branch of the superior laryngeal nerve extended to the interarytenoid muscle, the principal adductor of the posterior end of the vocal cord (fig. 3). When the nerve to this muscle, which may come from either the inferior or superior laryngeal nerve, is injured, adduction of the cords is about 50 per cent absent, and a marked change

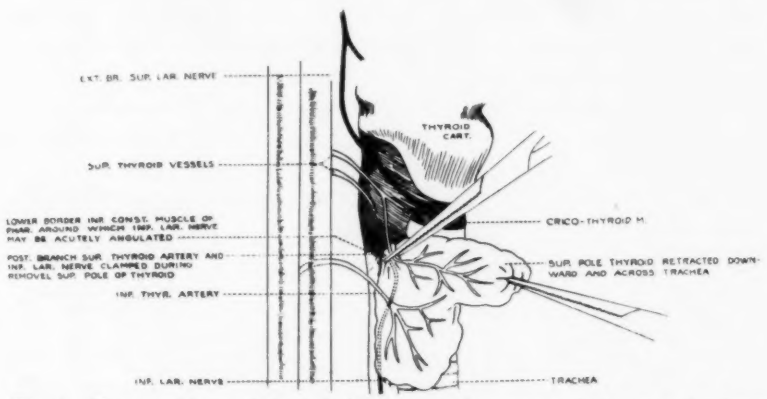
EXT. BR. SUP. LAR. NERVE
SUP. THYROID VESSELS
LOWER BORDER INF. CONST. MUSCLE OF PHAR. AROUND WHICH INF. LAR. NERVE MAY BE ACUTELY ANGULATED
POST. BRANCH SUP. THYROID ARTERY AND INF. LAR. NERVE CLAMPED DURING REMOVEL SUP. POLE OF THYROID
INF. THYR. ARTERY
INF. LAR. NERVE
THYROID CART.
CRICO-THYROID M.
SUP. POLE THYROID RETRACTED DOWNWARD AND ACROSS TRACHEA
TRACHEA

Fig. 4.—Note positions of the inferior laryngeal nerves and the posterior branch of the superior thyroid artery and how both may be crushed in hemostasis of this vessel.

in voice occurs, sometimes a total aphonia. In addition, there may be a loss of the sphincteric action of the upper part of the larynx which occasionally allows fluids to run through into the bronchi during the act of swallowing. This may also happen when the inferior pharyngeal constrictor muscle is paralyzed by injury to either the superior or inferior laryngeal nerve. This muscle elevates the larynx, sliding the glottis upward beneath the epiglottis during deglutition. The internal branch of the superior laryngeal nerve supplies sensation to at least the upper part of the larynx. When this nerve is involved in ligations of the upper pole, not only is anesthesia of the upper larynx produced but in addition there often occur: (1) interarytenoid or adductor paralysis with aphonia, (2) loss of upper laryngeal sphincteric action, (3) the

8. Vegus, V. E.: The Mechanism of the Larynx, London, William Heinemann, Ltd., 1929, p. 463.

thyromandibular reflex and (4) the vagopinna reflex. When anesthesia of the mucosa of the upper larynx occurs, the patient tolerates a pool of saliva resting on the vocal cords without coughing, and talks in a smothered tone as if the voice were coming through a mouth full of fluid. With this complication, there also may occur, as previously stated, an aspiration of fluids into the trachea or bronchi during the act of swallowing. The normal sensory nerve supply to the mucous membrane of the upper half of the larynx is an extremely important protective mechanism, producing, when irritated, a sphincteric action of the larynx above the vocal cords through contractions of the interarytenoid, thyro-arytenoid and lateral crico-arytenoid muscles, which are supplied by the superior and inferior laryngeal nerves.

The inferior laryngeal nerve, in passing upward, is closely attached to the posterior and relatively thinner border of the superior pole by interparenchymatous thyroid connective tissue, which is not the pretracheal fascia. This attachment is sometimes so firm that when the superior pole is pulled downward and across the trachea, it retains such a firm hold that the nerve not only becomes sharply kinked around the inferior borders of the inferior pharyngeal constrictor muscle and thyroid cartilage but may be detached from its terminal muscle beds (fig. 4). In addition, as previously stated, it may be so elevated from its posterior position that a hemostat could easily involve it when a branch of the superior or inferior arteries needs clamping along the posterior edge of the superior thyroid pole (fig. 4). I have found repeatedly, as Fowler and Hanson reported, that the inferior laryngeal nerve is not held attached to the posterior border of the thyroid gland by the pretracheal fascia. Judd [9] stated, in 1921, that he was under the impression that the inferior laryngeal nerve was frequently injured near its entrance into the larynx.

THE THYROMANDIBULAR REFLEX

The thyroid gland is supplied by sympathetic nerves which reach the gland as plexuses along the superior and inferior thyroid arteries from the superior and middle sympathetic cervical ganglions respectively. Branches, probably from the superior laryngeal nerve, are often seen to accompany the superior polar vessels along the anterior surface of the gland. When the superior thyroid vessels are ligated, under local anesthesia, the patient frequently complains of pain in the lower molar teeth on the corresponding side. Much more rarely pain is experienced along the lateral border of the tongue. The anatomic pathways of this reflex have, as far as I could determine, not been described. In considering the rôle of the autonomic neurons in visceral afferent and

9. Judd, E. S.: Ann. Surg. **73**:321, 1921.

efferent stimuli, it must be kept in mind that one preganglionic neuron enters into synaptic reactions with numerous postganglionic neurons, producing a wide radiation of efferent reactions from a single afferent stimulation. Every sympathetic ganglion receives fibers from more than one reflex arch in the spinal cord, and splanchnic or visceral sympathetic irritation may be relayed to somatic or peripheral sensory zones and vice versa.

The superior cervical sympathetic ganglion which sends fibers along the superior thyroid artery to the thyroid gland is connected, through gray rami communicantes, to the first four cervical spinal nerves. The sensory root of the trigeminal nerve is a long columnar neuropil known as the substantia gelatinosa, which extends downward through the posterior part of the medulla oblongata and upper spinal cord to the level of the second spinal nerve. It is the largest and most sensitive of all sensory roots and is attached intimately to the posterior or sensory horn of gray matter of the cord as low as the second spinal nerve. The

Fig. 5.—Approximating the anterior edges of the thyroid and cricoid cartilages raises the tone of the vocal cords; separating them, as in paralysis of the cricothyroid muscles, lowers the tone of the vocal cords. It may be possible to raise or lower the tone of the singing voice by a similar technic.

pathway of the thyromandibular, splanchnosomatic, sensory reflex quite likely originates on the sympathetic plexus of the superior thyroid artery, passing to the superior cervical sympathetic ganglion, from there to the first or second cervical posterior root ganglion by way of gray rami communicantes and from there to the posterior or sensory horn of the spinal cord, spilling or synapsing onto the substantia gelantinosa which sends somatic sensory impulses along the mandibular nerve to the lower molar teeth. Why it does not send sensory impulses through the ophthalmic and maxillary branches of the trigeminal nerve is a deeper physiologic and anatomic mystery. Therefore, when trauma to the superior thyroid artery produces pain in the lower molar teeth, one has a compounded nerve reflex which probably originates in a sympathetic arterial nerve plexus, passes through a sympathetic ganglion to the ganglion of a sensory root of a spinal nerve and then, instead of only an immediate somatic zone registration supplied by the usually correlating upper cervical nerves, a portion of the impulse jumps to the most highly sensitive sensory root of another (cranial) sensory nerve

and registers in the somatic or peripheral zone of the inframandibular branch of the trigeminal nerve. The superior cervical sympathetic ganglion is also connected with the petrosal ganglion of the glossopharyngeal nerve, to the ganglion of the root and trunk of the vagus, to the hypoglossal nerve and to the pharyngeal plexus. Keeping these connections in mind in addition to the connections with four upper sensory cervical spinal nerves, it may be better understood why patients complained of so much pain during superior polar ligations of exophthalmic goiters as frequently practiced previous to the era of preoperative preparation with iodine. The ligated poles sent impulses to sensory zones well above and below the locally anesthetized area.

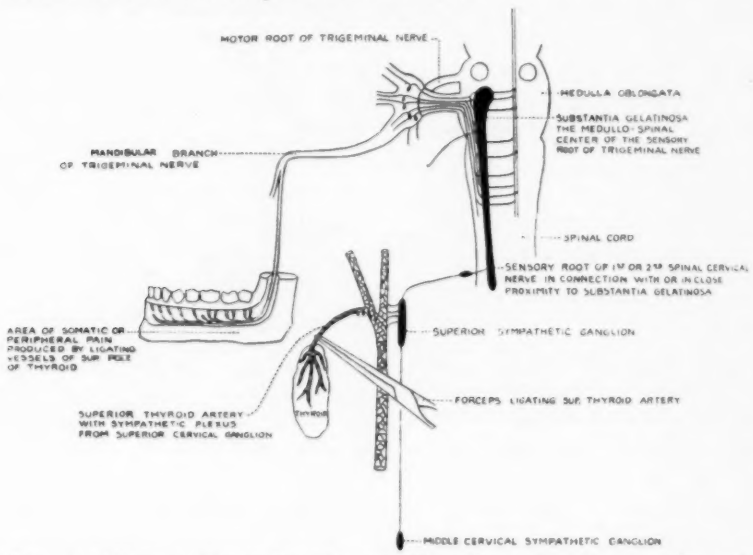
MOTOR ROOT OF TRIGEMINAL NERVE
MEDULLA OBLONGATA
SUBSTANTIA GELATINOSA THE MEDULLO-SPINAL CENTER OF THE SENSORY ROOT OF TRIGEMINAL NERVE
MANDIBULAR BRANCH OF TRIGEMINAL NERVE
SPINAL CORD
SENSORY ROOT OF 1ST OR 2ND SPINAL CERVICAL NERVE IN CONNECTION WITH OR IN CLOSE PROXIMITY TO SUBSTANTIA GELATINOSA
AREA OF SOMATIC OR PERIPHERAL PAIN PRODUCED BY LIGATING VESSELS OF SUP. POLE OF THYROID
SUPERIOR SYMPATHETIC GANGLION
FORCEPS LIGATING SUP. THYROID ARTERY
SUPERIOR THYROID ARTERY WITH SYMPATHETIC PLEXUS FROM SUPERIOR CERVICAL GANGLION
THYROID
MIDDLE CERVICAL SYMPATHETIC GANGLION

Fig. 6.—Diagram illustrating the possible reflex when the superior pole of the thyroid is ligated or clamped: the thyromandibular reflex.

THE VAGOPINNA REFLEX

When the superior laryngeal nerve is ligated, clamped or given an injection, particularly the internal branch, an occasional patient complains of pain in the external rim of the auditory canal and in the lower internal portion of the pinna. The reverse of this is true when the auditory canal is irritated, which often produces laryngeal irritation and coughing. The pathway of this first reflex originates in the superior laryngeal nerve, passing to the ganglion of the trunk of the vagus and from here out through Arnold's nerve which is an auriculovagus sensory somatic branch, the peripheral distribution of which terminates in anterior and posterior branches on the external ear or auricle.

The posterior branch of Arnold's nerve, which supplies the skin over the lower and internal surface of the pinna, is known as "alderman's nerve," owing to the treatment that the old governors of London accepted from their servants, who stroked the posterior surface of the external ears or pinnea of their masters with acrid and cooling solutions, alleviating in many instances the feeling of an overfilled stomach which these well satiated gentlemen contracted numerous times during a banquet of long duration. Stimulating the somatic sensory terminations of the posterior peripheral branch of Arnold's nerve sent a stimulus to the ganglion of the trunk of the vagus, which, in turn, promoted a much desired but then much more poorly understood peristalsis.[10]

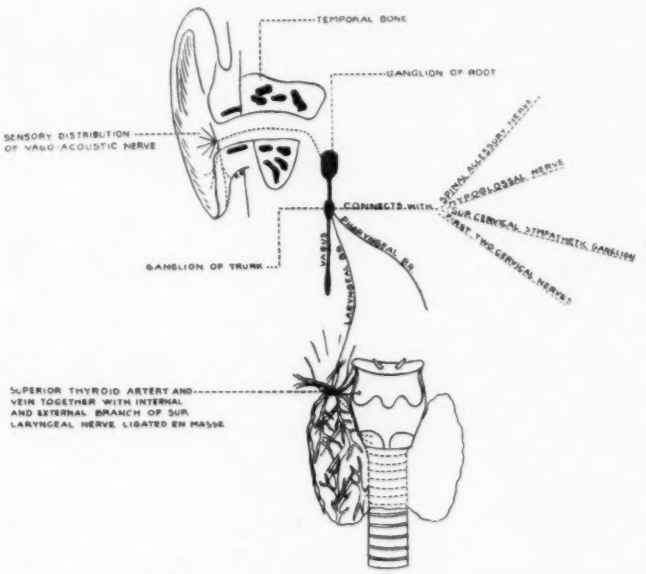
TEMPORAL BONE
GANGLION OF ROOT
SENSORY DISTRIBUTION OF VAGO-ACOUSTIC NERVE
CONNECTS WITH
HYPOGLOSSAL NERVE
FOUR CERVICAL SYMPATHETIC GANGLION
FIRST TWO CERVICAL NERVES
GANGLION OF TRUNK
PHARYNGEAL BR
LARYNGEAL BR
SUPERIOR THYROID ARTERY AND VEIN TOGETHER WITH INTERNAL AND EXTERNAL BRANCH OF SUP. LARYNGEAL NERVE LIGATED EN MASSE

Fig. 7.—The vagopinna reflex.

PARALYSIS OF THE SOFT PALATE

Not infrequently patients who have had bilateral ligations of the superior thyroid vessels, with or without resections, complain for twenty-four to forty-eight hours of fluids coming through their nostrils from the pharynx during the act of swallowing. Normally this is prevented by the soft palate's elevating muscles, the levator palati, which are supplied through the pharyngeal plexus by the accessory vagus nerve, which connects the plexus with the ganglion of the trunk of the vagus. In what manner or by what nerve paths the motor nerves supplying the levator palati muscles are interfered with following superior polar

10. Poynter, W. M.: Personal communication to the author.

vessel ligations is not understood. The superior cervical sympathetic ganglion and the superior laryngeal nerve may be involved, or a direct injury to the pharyngeal plexus is possible. Since this paralysis lasts for a day or two only, a reflex pathway is indicated.

The inferior constrictor muscle of the pharynx, one of an important group of muscles in swallowing and the principal elevator of the larynx, is innervated sometimes by the superior laryngeal nerve. If this muscle is involved, the cooperative muscular contractions of the constrictor may be absent during swallowing, resulting in a tardy or absent contraction of the elevating muscles of the soft palate, which may not of necessity be paralyzed.

OPERATIVE PROCEDURES

There has been no particular technic advocated or adopted for the liberation and resection of the superior pole of the goitrous thyroid. Kocher [11] may have been the first surgeon to advise a consideration of the superior laryngeal nerve. In August, 1928, before a meeting of the state societies of Wyoming, Montana and Idaho, held in Yellowstone Park, I reported my experience with the superior laryngeal nerve, which had extended back over a period of eight years. I reported also a technic for exposing the superior pole and vessels which avoided the branches of the superior laryngeal nerve.

In 1920, during an attempt to develop a new technic for bilateral resections of the goitrous thyroid and with a patient under local peripheral sensory nerve block, I exposed as a preliminary step both superior poles of a large goiter, which lay opposed to the thyrohyoid membrane. After placing a ligature around the upper end of one superior pole and its sheath, I noticed a moderate lowering of tone in the patient's voice as she complained of referred pain in the lower molar teeth on the corresponding side as well as pain in the pinna of the external ear. When a second ligature was placed around the upper end of the other superior pole, the patient experienced only the thyromandibular reflex, but could not speak, owing to an aphonia of about 90 per cent which lasted for four months. During this time, the posterior ends of each vocal cord failed to approach the midline due to an interarytenoid adductor paralysis, which in some instances persists for only four to six months. Since this experience, whenever a patient is under local anesthesia only, I have tested the voice and inquired about referred somatic pains as each polar set of vessels is ligated. These referred pains in the lower teeth have been noticed by other surgeons, but have not been dwelt on in the literature, to any extent at least. With the development of the technic to be described, the occurrence of

11. Kocher, quoted by Nordland (footnote 7).

changes in the tone of voice and referred pains has markedly decreased. In advanced cases of toxic thyroidism, when a psychic block is desirable through the use of light gas analgesia, a voice and referred somatic pain test during resection of the superior pole cannot be made. Since a psychic block in addition to a local peripheral sensory nerve block is practiced by many of the most experienced surgeons in this field, a technic is desirable that will avoid the branches of the superior laryngeal nerve, as well as the inferior, under any type of anesthesia.

During an operation under local anesthesia or after the patient is allowed to awaken from a psychic block produced by gas, a higher pitch to the voice may be obtained by approximating the cricoid and thyroid cartilages with a towel clip (fig. 5). In one case of bilateral cricothyroid paralysis, with a marked lowering of the singing voice, I wired the cricoid up beneath the lower border of the thyroid cartilage in an attempt to restore the patients voice to a higher tone (fig. 8). This

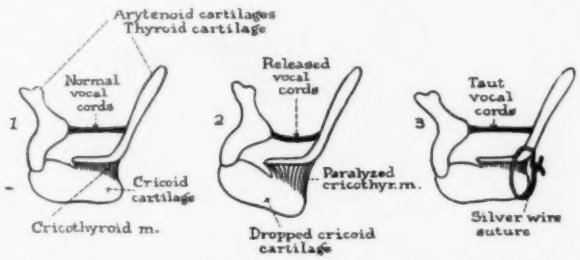

Fig. 8.—Lateral view of the thyroid and cricoid cartilages, including the vocal cords and cricothyroid muscles. In *2*, note the relaxation of the vocal cords when the cricothyroid muscle is paralyzed by injury to the external branch of the superior laryngeal nerve.

resulted in raising her voice to an undesirably high pitch which persisted for over six months. About one year after removal of the wire, the tone was lowered, but its previous clarity never completely returned. In singers a resection of a goitrous thyroid must be given due consideration relative to the superior as well as the inferior laryngeal nerve. There is a possibility of changing singing tones to a higher or lower pitch by elevating with a suture or depressing the cricoid cartilage through a paralysis of the cricothyroid muscles. Undoubtedly, many of the postoperative husky and lower voices result from injury to only the external branches of the superior laryngeal nerves.

TECHNIC OF SUPERIOR POLE RESECTIONS

The modified Kocher flap is used, which I described in *The Journal of the American Medical Association*.[12] This gives the greatest mobil-

12. Roeder, C. A.: Thyroidectomy, J. A. M. A. **79**:2066 (Dec. 16) 1922.

ity of the ribbon muscles without a transverse section. When it is necessary to cross-section these muscles, the sternomastoid muscle is first liberated by Lahey's method, and a modified Masten clamp (fig. 9) is then applied, which, after severing the muscles, gives ample exposure of the superior pole without the use of sharp pointed retractors or forceps. The superior thyroid vessels on the anterior surface of the superior poles are individually caught and ligated after the sheath has been split longitudinally (fig. 1). Each pole is then lifted from its bed in this sheath of pretracheal fascia, which leaves the superior laryngeal branches of the vagus and all adjacent nerve trunks uninjured. When a posterior branch of the superior thyroid artery is present, it is ligated well away from the inferior laryngeal nerve as it approaches the inferior borders of the inferior pharyngeal constrictor muscle and the

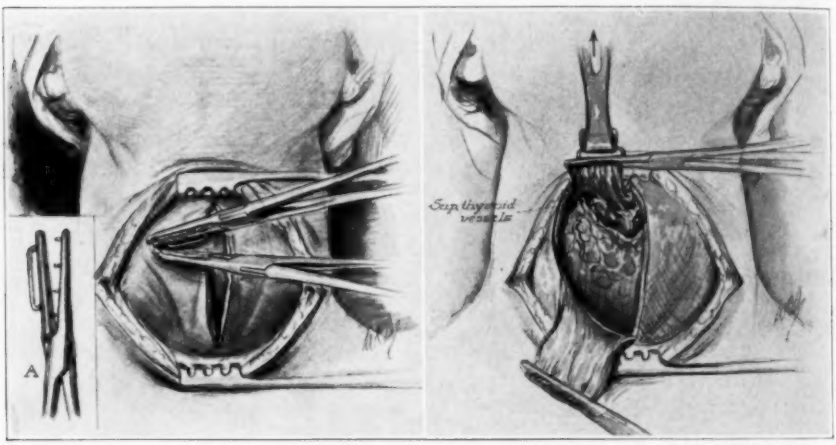

Fig. 9.—Modified Masten clamp for cross-sectioning ribbon muscles. Note the loop into which a retractor is placed, preventing slipping and tearing of the muscles. In most instances transverse section of ribbon muscles is not necessary, when the flap is made according to a technic described in 1922 (Roeder, C. A.: Thyroidectomy, J. A. M. A. **79**:2066 [Dec. 16] 1922).

thyroid cartilage, a technic which may leave occasionally a portion of the posterior edge of the superior pole over the upper end of the inferior laryngeal nerve. Care is taken not to pull the pole too far downward and across the trachea in order to avoid stretching or sharply angulating the upper extralaryngeal end of the inferior laryngeal nerve (fig. 4). Whenever a patient who is under only segmental or local anesthesia complains of pain in the somatic distribution of Arnold's nerve during ligation of the superior thyroid vessels, it is a positive warning that the superior laryngeal nerve is involved. When this reflex does not occur, however, it does not indicate that this nerve is not involved. From traction on the superior poles downward and across the trachea after

liberation from their sheaths, the patient's voice may suddenly change or disappear. If traction has not been too severe, the voice returns immediately. This is an indication of trauma to the inferior laryngeal nerve where it lies attached to the posterior border of the superior pole, or to sharp angulation of the nerve around the inferior border of the inferior pharyngeal constrictor muscle (fig. 4). It must be kept in mind that one or both inferior laryngeal nerves may be injured by traction on the superior poles, which may account for the unexplained cases of paralysis of the vocal cord following an operation that did not clamp or ligate the nerves. Traction downward on the superior pole before its sheath is liberated may injure the internal branch of the superior laryngeal nerve, producing an adductor paralysis (fig. 1).

CONCLUSIONS

During the removal of the superior pole of a goitrous thyroid, the following significant complications may occur:

(1) Injuries to the inferior and superior laryngeal branches of the vagus, producing:
   (*a*) Partial or complete loss of voice
   (*b*) Obstruction to inspiration
   (*c*) Aspiration of ingested fluids into the bronchi
   (*d*) Loss of sensation to the mucosa of the larynx
   (*e*) Referred pain to the lower portion of the pinna through the "vago-pinna reflex"

(2) Referred pain to the mandibular teeth through the "thyromandibular reflex"

(3) Paralysis of the soft palate

(4) Referred somatic pain through any or all of the first four cervical spinal sensory nerves

(5) Hemorrhage from the superior thyroid vessels

(6) Injury to or removal of parathyroid glandules

THE RÔLE OF PERIOSTEUM IN THE HEALING OF FRACTURES

AN EXPERIMENTAL STUDY *

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The rôle played by the various components of bone in the healing of fractures has been the subject of many researches since the work of Duhamel [1] in 1741. It is, of course, one of great practical importance as well as of theoretical interest. Because of the volume of the literature and the variety of opinions held, a classification of the theories of bone repair is quoted from Bancroft,[2] who has summarized this subject as follows:

1. The periosteal theory presupposes that the periosteum and endosteum are definite organs for bone formation and repair, and that the bone cells arise from them and from no other source.

2. The osteoblastic theory may be divided into two subtitles.

Type A. This assumes that in bone repair following injury bone cells are liberated from their lacunae and that they reproduce and form new bone.

Type B. This assumes that following injury wandering connective tissue cells, fibroblasts, are drawn into the area of trauma. Owing to the stimulus of the repair, they are transformed into bone producing cells and then become specific cells.

3. The extracellular deposition of calcium salts theory assumes that there is no definite bone producing cell; that following injury, possibly by positive chemotaxis, calcium salts in the proportions usually found in bone are deposited in the extracellular framework of connective tissue and that the connective tissue cell then becomes a bone cell by functional adaptation.

A more comprehensive view of this whole problem may be obtained from an inspection of figure 1. As can be seen, the controversy regarding the osteogenic property of periosteum is not a recent one. The first champion of periosteum as a bone-forming tissue was Duhamel.[1] He employed the method of feeding madder, which had been discovered five years before by Belchier.[1] The bones of animals fed on this alizarin-containing plant became red, because of the elective

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* From the Department of Orthopedic Surgery of the University of California Medical School.

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1. Quoted by Keith: Brit. J. Surg. **5**:685, 1918.

2. Bancroft, F. W.: Bone Repair Following Injury and Infection, Arch. Surg. **5**:646 (Nov.) 1922.

staining of the newly formed bone. Duhamel observed that the periosteum in the neighborhood of a fracture became greatly swollen, and was chiefly responsible for the formation of the repairing callus.

Opposed to the theories of Duhamel was John Hunter,[1] who was greatly influenced by the teachings of Haller. Haller and Hunter believed that the periosteum was merely a vascular covering that served for the nourishment of the bone. They were convinced that only the arteries had the ability to form bone. Hunter brought out the fact that two processes were at work together in the growth of bone, namely, deposition and absorption.

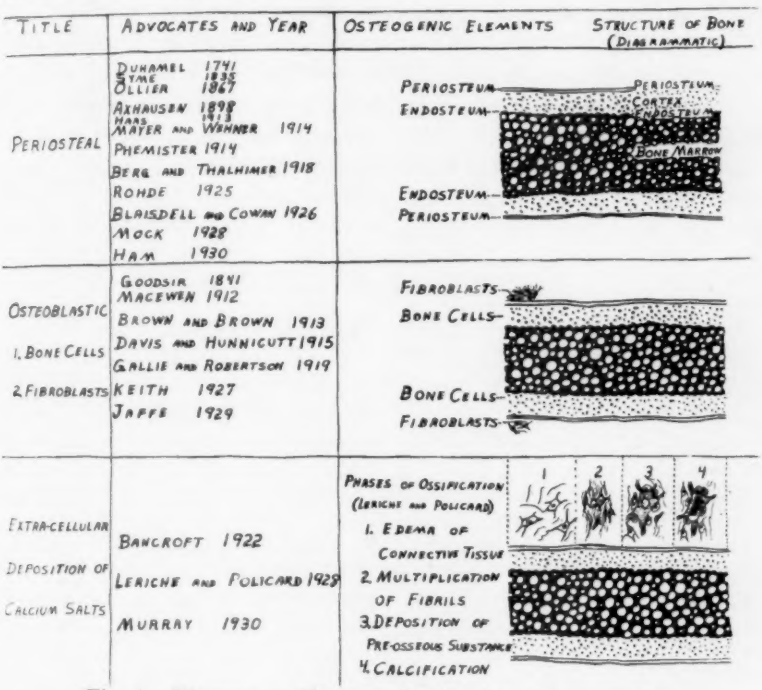

Fig. 1.—Diagram to illustrate the theories of bone repair.

To review all the experimental work that has been cited for or against the osteogenic function of periosteum would exceed the bounds of the present paper. It may suffice to enumerate the workers who have advocated each of the theories of the formation of bone. Since Duhamel, the primary rôle in this process has been assigned to the periosteum by Syme,[3] 1835; Flourens,[4] 1842; Ollier,[4] 1867; Axhausen,[5]

3. Quoted by Keith: Brit. J. Surg. **6**:19, 1918.

4. Quoted by Keith (footnote 3, p. 160).

5. Axhausen, G.: Die histologischen und klinischen Gesetze der freien Osteoplastik auf Grund von Thierversuchen, Arch. f. klin. Chir. **88**:23, 1909.

1909; Haas,[6] 1913; Mayer and Wehner,[7] 1914; Phemister,[8] 1914; Berg and Thalhimer,[9] 1918; Rohde,[10] 1925; Blaisdell and Cowan,[11] 1926; Mock,[12] 1928, and Ham,[13] 1930.

Following Haller and Hunter in a denial of the osteogenic function of periosteum, Goodsir[3] in 1845 first advanced the theory that bone cells ("corpuscles") had the power to form new bone. The next advocate of the osteoblastic theory was Macewen.[14] In 1912, he repeated many of the experiments of Ollier, obtaining different results, probably to be explained on the assumption that Macewen included less tissue in his removal of periosteum. Whereas Ollier had obtained a growth of new bone from periosteal transplants, Macewen was unable to find newly formed bone in such grafts, and noted the growth of bone from the surface of the cortex that had been denuded of periosteum.

Later supporters of the osteoblastic theory of bone repair include Brown and Brown,[15] 1913; Davis and Hunnicutt,[16] 1915; Gallie and Robertson,[17] 1919; Keith,[18] 1927, and Jaffe,[19] 1929. The term "osteoblastic theory" covers numerous rather divergent views of the growth of bone. Macewen believed that the bone cell of the cortex was the

6. Haas, S. L.: Regeneration of Bone from Periosteum, Surg., Gynec. & Obst. **17**:164, 1913.

7. Mayer, L., and Wehner, E.: An Experimental Study of Osteogenesis, Am. J. Orthop. Surg. **12**:213, 1914.

8. Phemister, D. B.: The Fate of Transplanted Bone and Regenerative Power of Its Various Constituents, Surg., Gynec. & Obst. **19**:303, 1914.

9. Berg, A. A., and Thalhimer, W.: Regeneration of Bone, Ann. Surg. **67**: 331, 1918.

10. Rohde, C.: Does Bone Form from Osteoblasts or from a Metaplasia of the Surrounding Connective Tissue? Surg., Gynec. & Obst. **41**:740, 1925.

11. Blaisdell, F. E., and Cowan, J. F.: Healing of Simple Fractures: An Experimental Study, Arch. Surg. **12**:619 (March) 1926.

12. Mock, H. E.: Periosteal Transplants in the Repair of Delayed Union, Ununited Fractures, and Loss of Bone Substance, Surg., Gynec. & Obst. **46**:641, 1928.

13. Ham, A. W.: A Histological Study of the Early Phases of Bone Repair, J. Bone & Joint Surg. **12**:827, 1930.

14. Macewen, W.: The Growth of Bone, Glasgow, James Maclehose & Sons, 1912.

15. Brown, W. L., and Brown, C. P.: Preliminary Report on Experimental Bone and Periosteal Transplantation, Surg., Gynec. & Obst. **17**:681, 1913.

16. Davis, J. S., and Hunnicutt, J. A.: The Osteogenic Power of Periosteum: With a Note on Bone Transplantation, Ann. Surg. **61**:672, 1915.

17. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, Brit. J. Surg. **7**:211, 1919.

18. Keith, A.: Concerning the Origin and Nature of Osteoblasts, Proc. Roy. Soc. Med. (Sect. Surg.) **21**:301, 1927.

19. Jaffe, H. L.: The Structure of Bone: With Particular Reference to Its Fibrillar Nature and the Relation of Function to Internal Architecture, Arch. Surg. **19**:24 (July) 1929.

active agent in the deposition of calcium salts. Hey Groves [20] pointed out that osteoblasts develop most rapidly in the haversian canals of a bone graft. In discussing the formation of bone in laparotomy wounds, Keith held that osteoblasts develop from the buds of capillary endothelium which invade the scar tissue.

The theory of the extracellular deposition of calcium salts, as described, is favored by Bancroft. Murray [21] has reported work that supports this theory. A recent book by Leriche and Policard [22] is devoted chiefly to the support of the thesis that bone is formed by the impregnation with calcium salts of an edematous connective tissue. This connective tissue first reverts to an embryonic state and then undergoes what these authors term a preosseous infiltration. Leriche and Policard expressed the belief that the chief function of the periosteum is to limit bone growth, although they conceded that it is a connective tissue medium favorable for the development of bone. In regard to the osteoblasts, these authors regarded them as osteolytic elements that represent reactionary attempts of the connective tissue cells against the preosseous transformation.

That the periosteum may hinder as well as assist the union of fractures had been pointed out by Cowan.[23] In a microscopic study of experimental fractures in dogs and kittens, this worker found that the ends of the fragments were sometimes prevented from fusing and reestablishing vascular communication by the ingrowth of dense avascular fibrous tissue from the periosteum. When a hole was drilled in the patella, it became plugged with fibrous tissue that apparently was continuous with the periosteum.

From a clinical standpoint, the question as to the osteogenic function of the periosteum is of importance chiefly in the healing of bone following fractures, and in the behavior of bone grafts. If the periosteum forms bone, every effort should be made to conserve it near fractures and on bone grafts. To determine the value of periosteum in the vicinity of fractures, a series of experiments was done on eight rabbits and two dogs.

METHODS

In general, the method followed was the production of a fracture or defect in each of two comparable bones of the same animal, with a different treatment of the periosteum on the right and left sides. The two radii in rabbits or the two fibulae in dogs usually were attacked. X-ray pictures of the operative sites were

20. Hey Groves, E. W.: Methods and Results of Transplantation of Bone in the Repair of Defects Caused by Injury or Disease, Brit. J. Surg. **5**:185, 1917.

21. Murray, C. R.: The Repair of Fractures, Minnesota Med. **13**:137, 1930.

22. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone, St. Louis, C. V. Mosby Company, 1928.

23. Cowan, J. F.: Non-Union of Fractures: An Experimental and Clinical Study, Ann. Surg. **88**:749, 1928.

made immediately following the operation and at weekly intervals thereafter until union occurred or the fact of nonunion was established clearly. The animals were then killed, and microscopic studies were made of the sites of operation. Sodium amytal, given intraperitoneally in dosages of 0.060 Gm. per kilogram of body weight, provided the anesthesia in all operations. Sterile technic was used, and incisions were closed with black silk and covered with dry dressings. No splints were necessary as the intact ulna or tibia prevented undue movement of the fractured bone. In no case did infection of the wound occur.

The experiments fall into four groups; the protocol of a typical experiment of each group is given.

Group A.—Saw cut in each radius, stripping periosteum on the left.

Rabbit 11 was a young adult weighing 2.3 Kg. The right radius was divided with a saw at the junction of its middle and distal thirds. The periosteum was incised transversely at the level of the saw cut, but was not otherwise disturbed. A similar saw fracture was produced near the middle of the left radius, and the periosteum was scraped from each fragment with a knife and periosteal elevator for a distance of 1 cm. on either side of the cut. X-ray pictures of both forelegs were taken immediately after the operation and at weekly intervals for six weeks. The animal was killed forty-three days after the operation, and microscopic sections of each radius were prepared. The results of all the experiments will be discussed together.

Rabbit 15 was subjected to a similar operation and was killed fifty-eight days after the operation. Roentgen and microscopic studies were made.

Group B.—Segment removed from each radius, stripping periosteum on the left.

Rabbit 21 was a young adult weighing 2.5 Kg. A segment 0.5 cm. in length was removed with its periosteum from the middle third of each radius. The periosteum on the fragments of the right radius was not disturbed. Both fragments of the left radius were denuded of periosteum for a distance of 1 cm. from the operative defect. X-ray pictures were taken following the operation, at weekly intervals for six weeks and at eight weeks. The animal was killed fifty-eight days after the operation, and microscopic sections were made through the sites of operation. Two other experiments of the same type were performed on rabbits 12 and 14, the former being killed after one hundred and seventy-three days and the latter after sixty-five days.

Group C.—Segment removed from each radius, drawing the periosteum over the ends of the right radius.

Rabbit 52 was a young adult weighing 2.5 Kg. The right radius was exposed; its periosteum was incised transversely at the middle of the shaft and was reflected back 0.5 cm. on either side of this point. A segment of radius, 0.3 cm. in length, was removed from the middle of this denuded area, after which the reflected flaps of periosteum were drawn back over the cut ends of the radius. A segment of equal length was removed with its periosteum from the middle third of the left radius. The periosteum was pushed back on each fragment of the left radius for a distance of 0.1 cm. from the defect, so as to prevent the periosteum falling over the ends of the radius. X-ray pictures were taken immediately after the operation and after fourteen, twenty-one and twenty-six days. The animal was killed after twenty-six days, and microscopic sections were made. Similar experiments were done on rabbits 40 and 49, but in these animals the condition was allowed to progress further, namely, fifty-eight and sixty-eight days.

Group D.—Segment removed from each fibula of a dog, drawing the periosteum over the ends of the right fibula.

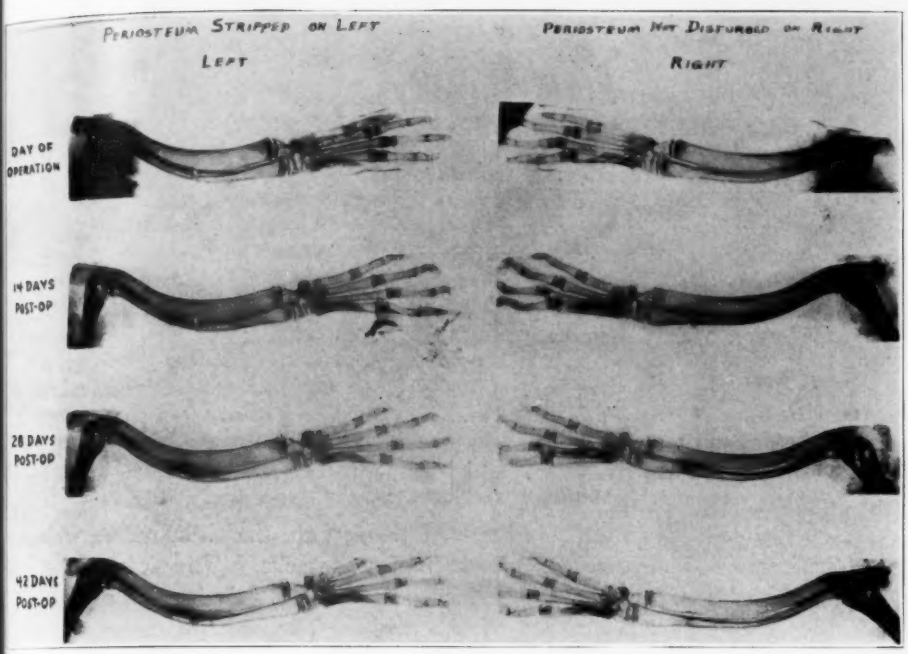

Fig. 2 (rabbit 11).—Series of postoperative roentgenograms.

Fig. 3 (rabbit 11).—Photomicrograph of left radius at the point of attachment of the periosteum.

Dog 41 was a large adult. The right fibula was exposed by a lateral incision splitting the fibers of the peroneus longus muscle. The periosteum was incised transversely at the junction of the middle and distal thirds of the fibula and was reflected to expose a segment of fibula 0.4 cm. in length, which was excised. The reflected flaps of periosteum were then drawn over the cut ends of the right fibula. The left fibula was exposed, and a segment 0.4 cm. in length was removed at the junction of its middle and distal thirds. The periosteum on the fragments of the left fibula was pushed back 0.1 cm. from the cut surface. X-ray pictures of both fibulae were taken after the operation and at intervals of four, five, seven, nine and eleven weeks. The animal was killed seventy-nine days after the operation. Gross examination showed a fibrous union of the left fibula, whereas no union had occurred in the right fibula. Microscopic sections were made. In another dog, no. 43, a similar experiment was performed, and the animal was killed after ninety-one days.

RESULTS

Group A.—In the two cases of this group, the right radius, with periosteum undisturbed, united in four weeks. The left radius, with periosteum stripped back from the saw cut, failed to unite across the outer cortex at the end of six weeks. The layer of cortex adjacent to the ulna united, possibly because the two bones of the rabbit's foreleg are very close together, so that the periosteum of the ulna is necessarily irritated by any operation on the radius (fig. 2). Microscopic examination of the left radius confirmed the impression given by the x-ray pictures. No newly formed bone was seen on the surface of the cortex until the point of attachment of the remaining periosteum was reached. Here subperiosteal callus could be seen (fig. 3).

Group B.—In the three cases comprising this group, the gap in the right radius was completely closed in one, almost closed in another and about one-half closed in the third. Microscopic section showed an active production of subperiosteal callus in each of these cases. On the contrary, the left radius, from the ends of which the periosteum had been stripped, presented no attempt at callus production in any case, as observed by roentgen examinations (fig. 4) and microscopic section (fig. 5). Each of the three cases gave the typical picture of nonunion with tapering ends of bone projecting into fibrous tissue.

Group C.—In the three rabbits of this group the gap in the left radius was filled with new bone in four weeks. At the end of twenty-six days the fracture in the right radius showed by x-ray pictures (fig. 6) and microscopic examination (fig. 7) the typical picture of nonunion. In the two experiments lasting fifty-eight and sixty-five days there was a partial union of the fractures in the right radius because of the production of endosteal callus, but the external portions of the cortex failed to unite.

Group D.—Two dogs were used. In dog 41, the x-ray pictures (fig. 8) showed a tonguelike process of new bone growing upward

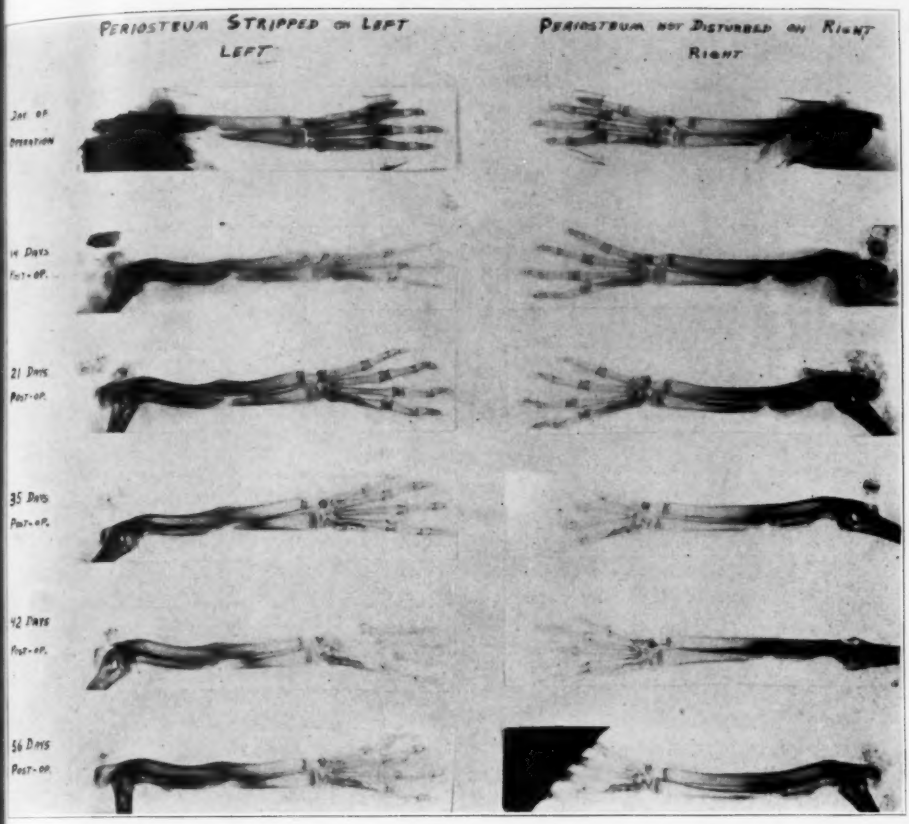

Fig. 4 (rabbit 21).—Series of postoperative roentgenograms.

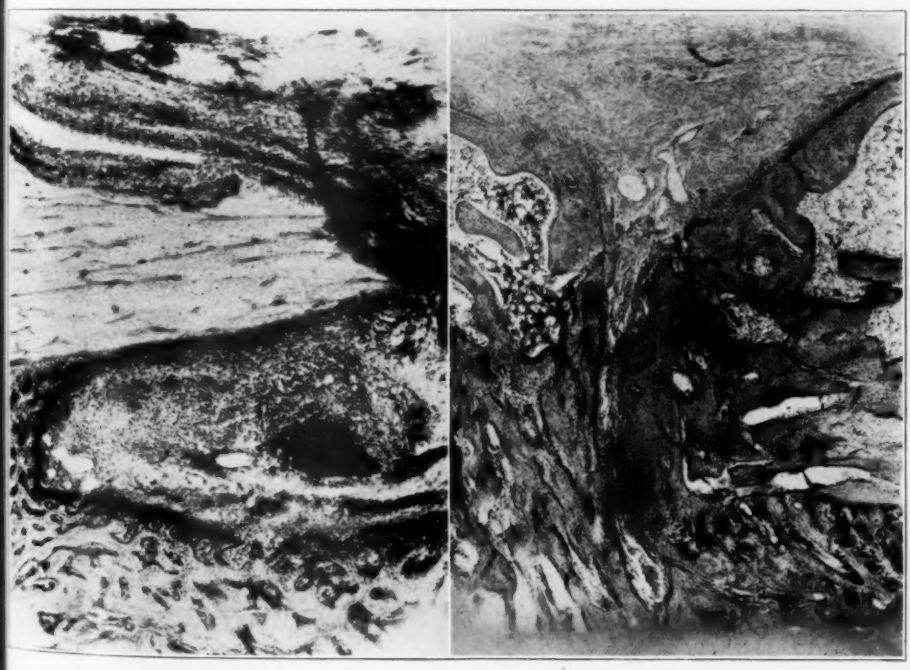

Fig. 5 (rabbit 21).—Photomicrographs of both radii. The section on the left is from the left radius; that on the right, from the right radius.

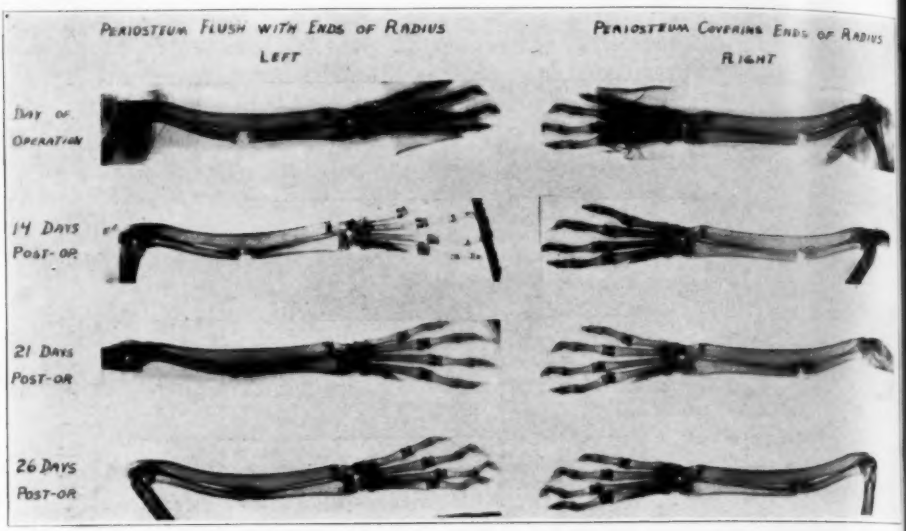

Fig. 6 (rabbit 52).—Series of postoperative roentgenograms.

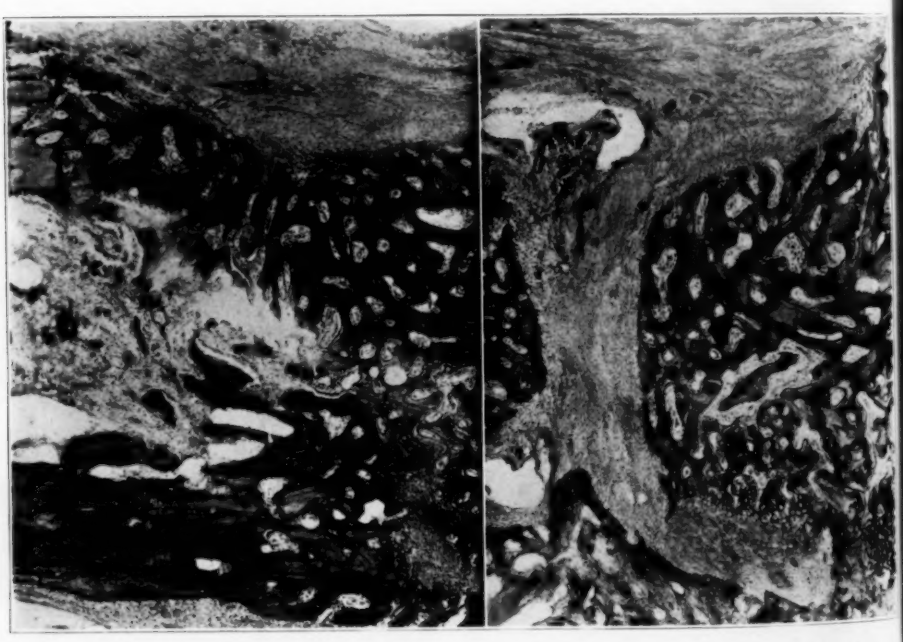

Fig. 7 (rabbit 52).—Photomicrographs of both radii. The section on the left is from the left radius; that on the right, from the right radius.

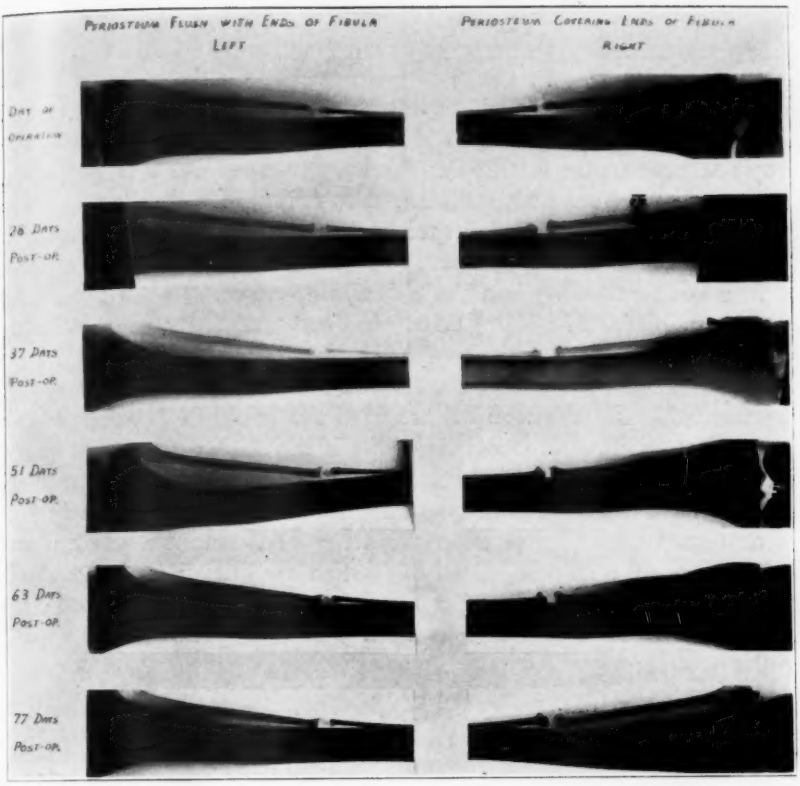

Fig. 8 (dog 41).—Series of postoperative roentgenograms.

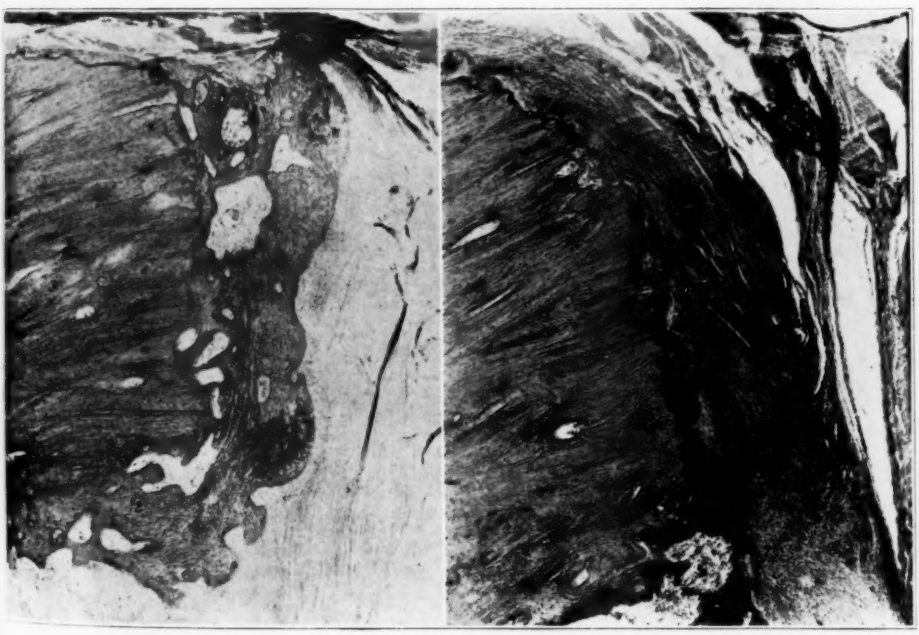

Fig. 9 (dog 41).—Photomicrographs of both fibulae. The section on the left is from the left fibula; that on the right, from the right fibula.

from the distal fragment of the left fibula, beginning after four weeks, and not quite bridging the gap at the end of eleven weeks. In microscopic sections of the left fibula (fig. 9), new bone was seen projecting into the defect from both fragments but failing to close the gap. The right fibula presented a bulbous thickening of the end of each fragment, with no effort to close the defect. In microscopic sections, the absence of new bone extending into the gap was apparent. In the other case, dog 43, the defects in both fibulae remained completely open, probably as a result of the interposition of muscle tissue.

These experiments demonstrate the two conditions necessary for the formation of periosteal callus: first, the presence of the cambium layer of the periosteum, and second, the separation of a part of the periosteum from the cortex, thus permitting the accumulation of blood between periosteum and cortex. The value of animal experimentation as compared with clinical observation lies in the normal control possible in the experimental animal but not in the human subject. While different species vary somewhat as to the rate of healing of bone, the general principles obtained from a study of one species can be applied to the others.

CONCLUSIONS

1. Periosteum plays the chief rôle in the healing of fractures.

2. Endosteal (medullary) callus aids in the healing of fractures, but in the absence of periosteum is often unable to complete the union.

3. The interposition of periosteum between the ends of a fractured bone may result in nonunion.

THE ANATOMY OF THE GASSERIAN GANGLION

ITS RELATION TO TIC DOULOUREUX *

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LEIDEN, HOLLAND

Before 1900 the surgical treatment for tic douloureux consisted of removal of the gasserian ganglion. Since that time a number of different procedures have been advocated. Spiller (1898) was the first to propose division of the root posterior to the ganglion. Frazier performed this operation in 1901. Korteweg,[1] in 1899, was the first to divide the root. The patient operated on by Korteweg was relieved from pain for twelve years, when it reappeared over the distribution of the first branch. In 1919, Frazier divided only the sensory root, thus preserving the motor division. In 1927, Zaayer [2] used a more radical procedure. He preserved the motor root, but extirpated the ganglion. Frazier,[3] in 1915, performed a partial division of the sensory root.

As a result of phylogenetic and embryologic studies, Frazier came to the conclusion that the peripheral branches of the ganglion were represented in the mesial, central and lateral thirds of the sensory root, a definite topographical relation existing. In discussing the phylogeny, Frazier referred to van Valkenburg's studies. Van Valkenburg [4] pointed out that in certain animals the fibers of the ophthalmic division are definitely separated from those of the maxillary-mandibular division. Frazier [5] observed in certain lower forms, reptiles and fishes, that the ophthalmic division has a separate ganglion. The embryologic studies made by Whitehead [5] showed that in the human embryo the ophthalmic part of the ganglion is separated from the principal part of it by a greater or less distance, and that the fibers

* Submitted for publication, July 30, 1931.

* From the Surgical Clinic of Professor Zaayer.

1. Korteweg: Algemiene Beschouwingen over de heelkunlige behandeling van ziekten van het centrale en het zenuwstelsel, Geneesk. Bl. mit Klin. en Lab. V. de prakt., Haarlem **17**:261, 1913-1914.

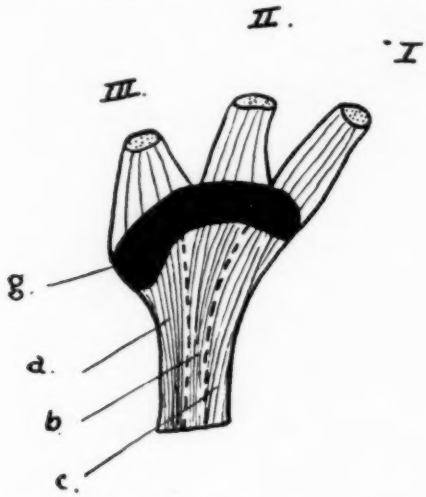
2. Zaayer: Arch. f. klin. Chir. **152**:76, 1928.

3. Frazier, C. H.: Subtotal Section of the Sensory Root for Relief of Major Trigeminal Neuralgia, Arch. Neurol. & Psychiat. **13**:378 (March) 1925.

4. van Valkenburg: Folia neuro-biol., 1911, vol. 5.

5. Frazier and Whitehead: The Morphology of the Ganglion Gasseri, Brain **48**:458, 1925.

of the sensory root run parallel and become arranged in separate bundles by the enveloping supporting tissue and do not tend to intermingle. He gave the following description of the ganglion in an embryo of twenty-eight weeks. The fibers of the sensory root emerge from the hilus of the ganglion as numerous small bundles. These bundles, as they pass upward toward the pons, run more or less parallel, with very little interchange of fibers. He described in older specimens the centripetal fibers as passing centrally in corresponding anatomic thirds of the sensory root. I have not had access to Frazier's[6] paper, but his opinions are clearly given in the following report: "Anatomisch verlaufen im Ganglion wie in der sensibelen Wurzel die Bahnen der drei Trigeminusäste völlig getrennt von einander und schon



Figs. 1.—Schematic form of the sensory root. In this and the following legends, I stands for ophthalmic nerve; II, maxillary nerve; III, mandibular nerve; *g*, ganglion semilunare; *a*, mandibular part of the sensory root; *b*, maxillary part of the sensory root, and *c*, ophthalmic part of the sensory root.

mit blossem Auge kann man in dem sensibelen Anteil des Ganglionstammes die entsprechenden Stränge zu den Unterabteilungen, resp. den drei Ästen verlaufen sehen. [Anatomically, the channels of the three branches of the trigeminus take the same course in the ganglion and in the sensory root, namely, they are entirely separated from one another, and even with the naked eye one can see in the sensory portion of the ganglion trunk the course of the respective strands to the subdivisions or to the three branches.]" Nothing was found in Frazier's article concerning the structure of the sensory root in adults.

6. Frazier, quoted in Zentralbl. f. Chir. **32**:16, 1925.

I have studied the structure of thirty-eight ganglions. These were removed from cadavers.[7]

In none of the ganglions examined were there three anatomically separated parts in the sensory root that corresponded to the three terminal divisions of the fifth nerve. One sensory root, when viewed

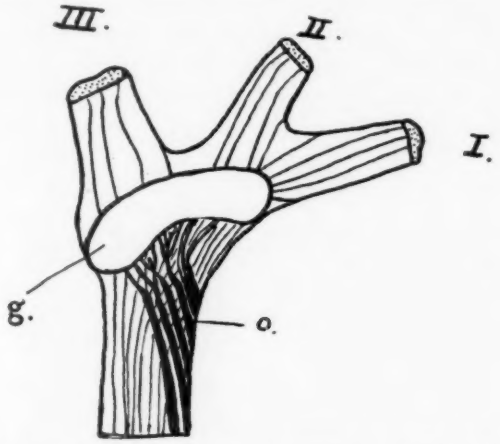


Fig. 2.—Schematic form of the sensory root showing the interlacing bundles of fibers; *g*, ganglion semilunare, and *o*, crossing bundles.

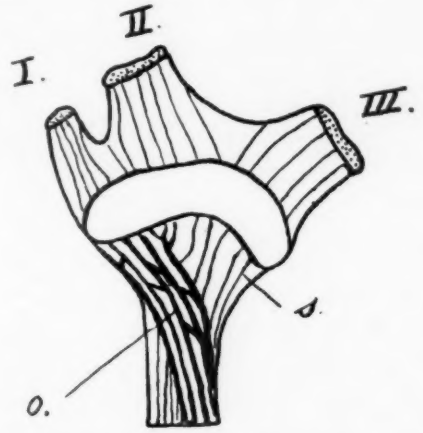


Fig. 3.—Interlacing bundles of fibers are shown here also; *o*, crossing bundles, and *s*, sensory root.

superficially, seemed to have three parts, but more careful examination showed that no division corresponding to the three terminal branches existed.

7. For the technic and more complete details the reader is referred to: Een onderzoek naar de samenstelling van het Ganglion Gasseri in verband met de operatieve behandeling van de Trigeminus-neuralgie, Dissertation, Leiden, 1929.

In a sensory root constituted according to Frazier's [8] idea, a bundle running, for example, in the medial third of the root would not cross at once to the lateral or central portion (figs. 2 and 3). This relation was not found by me to be constant, for in eight instances the fiber bundles crossed from one side of the root to the other.

In hardly any of the sensory roots examined did the bundles run parallel, with very little interchange of fibers. On the contrary, there were, as a rule, many anastomosing and interlacing fibers (fig. 4).

As a rule, the ramifications and anastomoses were most numerous at the hilus of the ganglion, where in some cases there was such a network of fibers that one would be justified in speaking of it as a

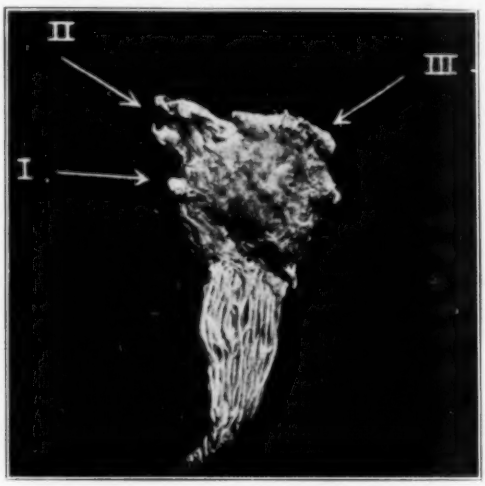


Fig. 4.—Photograph of a sensory root showing anastomosing and interlacing fibers.

plexus. This corresponds to Krause's [9] description: "Sobald der Stamm des Trigeminus durch den Schlitz den Duralsack verlassen hat, verbreitet sich die sensibele Wurzel indem die ursprünglich parallelen Faserbündel auseinenderweichen und sich durch zahlreiche Anastomosen zu einem engwachsigen Geflechte dem Plexus triangularis verstricken welches unmittelbar in das Ganglion gasseri übergeht. [As soon as the trunk of the trigeminus, through the cleft, has left the dural sac, the sensory root becomes broader, in that the originally parallel fiber bundles become separated and interlace by numerous

8. Frazier, C. A.: Operation for Radical Cure of Trigeminal Neuralgia. Analysis of Fifty Cases, Ann. Surg. **88**:534, 1928.

9. Krause, F.: Die Neuralgie des Trigeminus nebstder Anatomie und Physiologie des Nerven, Leipzig, F. C. W. Vogel, 1896.

Fig. 5.—Photograph showing interlacing of the pathways of the ophthalmic and maxillary divisions of the sensory root. The central bundle in the root received fibers from all the three parts of the ganglion.

Fig. 6.—Photograph of a sensory root showing plexus fibers without any regular arrangement.

anastomoses to a closely woven network, the plexus triangularis, which immediately passes into the gaserian ganglion.]"

Most of the ramifications and anastomoses were found in the medial half of the sensory root. The pathways of the ophthalmic and maxillary divisions interlace a great deal (fig. 5).

In most cases some fiber bundles emerged from the maxillary-mandibular portion of the ganglion to join the motor root (fig. 7).

I have also attempted to learn something about the formation of the ganglion itself. Serial sections of the ganglion were made. There

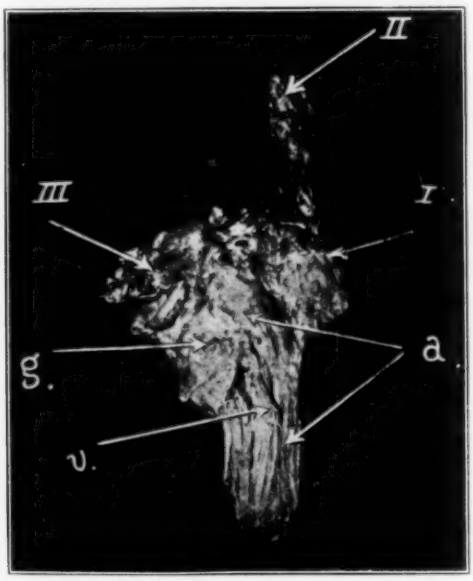


Fig. 7.—Photograph showing fibers bundles emerging from the maxillary-mandibular portion of the ganglion to join the motor root; *g*, ganglion; *a*, motor root, and *v*, two slight fiber bundles joining the motor root.

was no indication that the cell groups represented separate units, or that the interstitial tissue separated definite nerve bundles.

Comparing my findings with those of Frazier, I am unable to agree with his conclusions. Frazier's conclusions are based on the ganglion of the fetus and not on the fully developed ganglion of the adult. It is also certain that in the sensory root of the adult the fibers have no definite parallel arrangement. Certain schematic drawings that have been shown in different articles would indicate that this is the case.

The structure of the sensory nerve varies between two extremes. In one extreme, the bundles may have a parallel course, maintaining the same relation with other bundles throughout the length of the root,

illustrated in figure 1, a schematic form given by Frazier, which I have not found. At the other extreme is an arrangement in which there are no bundles running parallel, but only plexus fibers without any regular arrangement (fig. 6). Between these two extremes many variations may be found. Sensory roots may be found with interlacing bundles of fibers (figs. 2 and 3) and with bundles running practically parallel, but anastomosing frequently and in large numbers.

Dandy,[10] as the result of clinical observations, has come to the same conclusions. In twenty-three cases of tic douloureux in which total section of the sensory root had been made near the pons, he found that only four showed total anesthesia of the skin area supplied by the nerve. In the remaining nineteen more or less sensation was preserved, but there were marked variations in the amount. In three cases all forms of sensations were preserved over the distribution of all branches to about the same degree. The pain of the tic had, however, never reappeared. Dandy, furthermore, stated that after partial section of the root there is not any relation between the part of the sensory root divided and the sensory alterations that follow. The following case was cited by Dandy: The operation of partial section of the sensory root was performed near the pons for pain over the distribution of the supra-orbital nerve. After the operation the sensations of heat and cold were slightly diminished over the distribution of the three branches. The sensations of touch were quite normal. Dandy's conclusions were as follows: "Observations, such as described, deny the hypothesis that the peripheral branches are accurately represented by subdivisions of the sensory root."

Dandy cut the root near the pons, so, with the results cited, the only conclusion that can be arrived at is that the fibers change their position in the distance between the ganglion and the point at which the section is made. Further research will solve the problem.

CONCLUSIONS

1. The sensory root of the fifth nerve is not composed of three parts that correspond to the three peripheral branches from the gasserian ganglion.

2. The operation of partial section of the sensory root, assuming that the pain is carried by bundles having a definite location, is not based on anatomic facts, and therefore cannot be regarded as an absolutely reliable procedure.

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10. Dandy, W. E.: An Operation for the Cure of Tic Douloureux; Partial Section of Sensory Roots at Pons, Arch. Surg. **18**:687 (Feb.) 1929.

THE BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

II. OBSERVATIONS ON A STANDARD DIET *

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It is our purpose in this paper to consider the healing strength of the fractured fibulae of rats on a standard diet. In a preliminary report on this subject, two of us (Dr. Lindsay and Dr. Howes)[1] presented an original method for the determination of the healing strength of fibular calluses in rats from the inception of the fracture to the restitution of normal strength in the healing bone. The findings obtained at that time were in several instances later found to be either inadequate or inconclusive. However, on the basis afforded by this first contribution, the work has been carefully repeated with the result that a much better comprehension of the problem has been made possible. In some instances, important changes were made in technic, while in all cases the factors concerned have been clarified to a greater extent than existed before.

PROCEDURE

We found early that the age and weight range of the rats used in the preliminary work gave too great a disparity in our results; consequently, males from known stock, aged 4 to 8 months, and weighing between 190 and 300 Gm., were eventually chosen for experimentation. As noted in the first paper, the fibula of the rat proved ideal for our purpose for it was firmly splinted by the tibia (fig. 1). As was described previously, the fibula was fractured under aseptic conditions at a point opposite the most prominent point of the crest of the tibia, which we have designated as the "tibial prominence," and the healing strength observed from the sixth to the forty-fifth days postoperatively, at the expiration of which time the fracture was found to be firmly healed. In the case of the animals with fracture, the breaking strength only of the bone was determined. The diet

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* From the Department of Surgery, Yale University School of Medicine.

* The expenses of this investigation were defrayed by Davis and Geck, Inc.

1. Howes, Edward L., and Lindsay, Merrill K.: The Breaking Strength of Healing Fractures, J. Bone & Joint Surg. **13**:491 (July) 1931.

was the same as in the preliminary experiment, and in a similar manner relatively complete metabolic data were kept on all animals.

After being on the standard Moise and Smith [2] diet for one week, the animals were divided into three groups. The first group of fifty rats was free from fracture. At the end of the one week on the diet, they were killed, and the breaking strength of the left and right fibulae was determined. This group was designated the normal normals, and the breaking strength of their fibulae is considered to be the normal breaking strength of unfractured fibulae of rats within similar age, weight

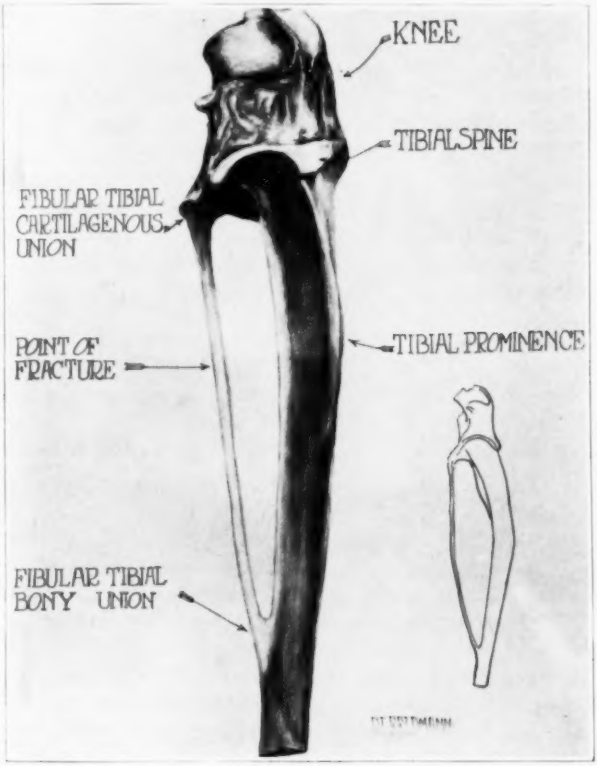

Fig. 1.—Fibula and tibia of the rat. Splinting of the fractured fibula is unnecessary as the tibia holds the fragments in good position.

and dietary limitations. Throughout all the experiments to be undertaken it is hoped that the findings obtained on these animals will serve as a basis on which to compare any other given result.

The second group, known in this paper as the standard controls, resembled the normal normals in that they were free from fracture, but differed in that they were continued on the diet for a greater length of time. These animals were used to determine the effect of the diet on the strength of normal bone. A division of the

2. Moise, T. S., and Smith, A. H.: Diet and Tissue Growth: I. The Regeneration of Liver Tissue on Various Adequate Diets, J. Exper. Med. **40**:13, 1924.

standard controls into lots of four was made at the time they were placed on the diet. Beginning on the thirteenth dietary day, and continuing at intervals of three days thereafter to the fifty-second day, one lot was killed for each interval. As will be noted, seven rats with fractured fibulae were killed simultaneously with each four of the standard controls without fracture. Consequently, it was felt advisable to adopt the postoperative intervals for both the animals with and without fracture. These intervals began on the sixth postoperative day and continued every third day thereafter to the forty-fifth day. In other words, there were fourteen postoperative intervals or time periods in which breaking strength determinations were made on four standard controls, as well as on the seven standard animals with fracture to be described.

The third and final group was known as the standard animals with fracture. This group consisted of lots of seven rats, each of which had been on the diet for one week. At the expiration of that time, the right fibula of every animal was fractured in the manner described in the first paper, and a lot of seven animals was

TABLE 1.—*Daily Drying Weights in Grams of Six Pair of Leg Bones of Normal Rats*

	Pair A	Pair B	Pair C	Pair D	Pair E	Pair F
First day (original weight)	1.580	1.365	1.365	1.650	1.590	1.270
Second day	0.845	0.865	0.825	0.990	0.935	0.730
Third day	0.840	0.845	0.819	0.988	0.922	0.726
Fourth day	0.828	0.843	0.817	0.984	0.913	0.715
Fifth day	0.822	0.840	0.815	0.980	0.911	0.709
Sixth day	0.818	0.838	0.809	0.977	0.909	0.704
Seventh day	0.817	0.834	0.802	0.975	0.906	0.701
Eighth day	0.814	0.830	0.800	0.974	0.904	0.700
Ninth day	0.813	0.828	0.798	0.974	0.903	0.702
Tenth day	0.813	0.827	0.798	0.972	0.901	0.702
Eleventh day	0.814	0.827	0.797	0.974	0.904	0.702
Twelfth day	0.814	0.828	0.799	0.974	0.903	0.703

assigned to each of the fourteen periods from the sixth to the forty-fifth postoperative days. Thus four standard controls controlled seven standard animals with fracture for each of the fourteen periods observed.

On the sixth postoperative day, and at intervals of three days thereafter, the seven standard animals with fracture and the four standard control animals for each period were killed. Measurements of body length, tail length and total length were taken and filed in our laboratory records. Whenever gross pathologic process other than that associated with the fracture was found, the animal was discarded and replaced by another. The fibula and tibia were next prepared as previously described [1] and appeared as in figure 1 when cleaned. It was decided that hereafter a complete histologic examination would be made on all fractures, and this will be reported at a later date. Due to this decision, five pairs of leg bones of the standard rats with fracture were placed in the desiccator over fresh anhydrous calcium chloride, while two pairs were preserved in a diluted solution of formaldehyde, U. S. P. (1:10) for histologic examination. All fifty of the unfractured normal normal bones were made ready for drying in a manner similar to the foregoing, but none were preserved for histologic study. We became interested in determining the optimum drying time for all these bones as we desired a dry bone and not one wet or "green" which would bend before breaking. We found that drying for seven to ten days removed practically all the moisture from the bones and proved sufficient for our purpose (table 1).

A roentgenogram of one representative fracture from each seven in the particular interval in question was taken, following which the fibular length of every bone was measured and recorded. After drying and measuring the fibulae, the breaking strength was determined on the fibulae of the fifty normal normals, the standard controls and the standard groups with fracture by the technic described in the first paper. In each instance, the strength of both right and left fibulae was noted. The observations were recorded and when indicated were rechecked on additional animals.

The correlations noted in the preliminary report on animal weight, fibular length and breaking strength were gone into in detail. On the basis of these correlations, a formula that we believe to be of considerable value was evolved.[3] By its use the disparity in the breaking strength results produced by the variance in weight of the animals selected was considerably reduced. This formula we found of value, not only in interpreting the breaking strength of the normal normals, but of both other groups as well.

Gross photographic studies presenting a picture of the developing callus as seen end on following the breaking of the callus in the beam testing machine were made, and though of some value, did nothing to add to our knowledge. Consequently, they were discarded. Likewise, an attempt to measure the callus of each fracture was discontinued because it did little more than agree with the impression one gained much more comprehensively from the roentgenographic studies. The animal weights and the food intake were again observed, and at this point the notation made in the preliminary paper is worth reiterating; namely, that we have constantly realized that our animals were not in a state of dietary equilibrium after being on the standard diet for but one week. However, our purpose remains to approximate clinical conditions as closely as possible with the material available.

RESULTS

A consideration of the experimental findings is divisible into three phases, i. e., those of the normal normal series, of the standard control lot and of the standard groups with fracture.

I. *The Normal Normal.*—Owing to the range in the weight of the animals of from 190 to 300 Gm., as well as to the differences in age, and other factors, it soon became evident that though we had limited the variables to a greater extent than in the preliminary report, we must develop some common basis on which a more thorough interpretation of the results could be made. This was eventually accomplished through correlations between animal weight, fibular length and breaking strength.

A. Correlation of Fibular Length to Breaking Strength: When all animals with fibulae of the same length were placed in groups, and the respective breaking strength of each fibula in each group added, and the arithmetical mean for the group, as well as the combined arithmetical mean for the left and right fibulae in each group determined, it was observed that there was a steady increasing progression in the breaking strength concomitantly with increasing fibular length. This is clearly seen in table 2.

3. William R. Thompson of the department of pathology aided in developing this formula.

On the basis of this it became evident at once that the greater the fibular length, the greater the breaking strength, and from this we plotted the curve seen in figure 2.

B. Correlation of Fibular Length to Animal Weight: Using the same fibular length groups as in the first correlation, we placed under each group the respective weight of the animal concerned. The results are shown in table 3.

From this we note that the longer the fibulae, the heavier the animals. This has been plotted in figure 3.

C. Correlation of Breaking Strength to Animal Weight: It would seem that if length and strength, and length and weight were positively correlated, a similar positive correlation should exist between the

TABLE 2.—*Correlation Between Fibular Length and Fibular Strength* *

	Fibular Length							
	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of breaking strength...	411	358	441	459	460	454	533	495
Combined mean for left and right fibula	384		450		457		509	

* Refer to table 2a for complete data.

TABLE 3.—*Correlation Between Fibular Length and Animal Weight* *

	Fibular Length			
	2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.
Arithmetic mean of animal weight.....	209	230	251	284

* Refer to table 3a for complete data.

strength and weight. However, this proved by far the most difficult of the three to demonstrate, but was indicated in an arbitrary division of the animals into four groups according to weight, i. e., from 190 to 225 Gm., 226 to 250 Gm., 251 to 275 Gm. and 276 to 300 Gm. In each respective group, the arithmetic mean of the breaking strength for all animals in the group was determined, and a progression found. The results of this are seen in table 4.

The plotted means seen in figure 4 show a steady increase in the breaking strength from the first to the last weight group. Similar correlations were found to exist when a different weight grouping was used, but in the majority of instances they did not show such clearcut results as the one used.

Our results then demonstrated that a correlation existed in each instance between the fibular length, the fibular breaking strength and the animal weight for the fifty animals observed. We have noted earlier that it was our purpose to reduce the breaking strength on all

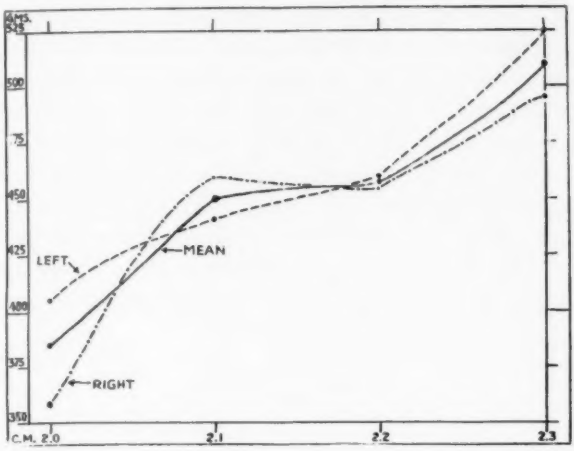

Fig. 2.—Correlation between breaking strength and the length of the right and left fibulae with the combined mean of their breaking strength for normal normal rats. The correlation shows that the longer the fibula is, the greater its strength. The curve of the mean between 2.0 and 2.1 cm. should lie between the curves of the right and left.

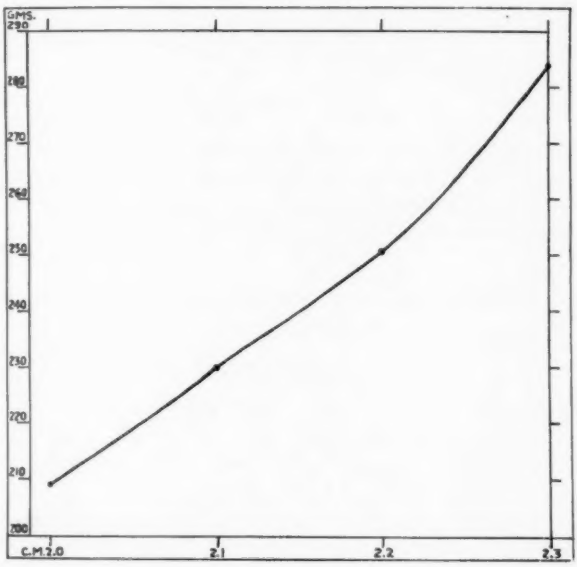

Fig. 3.—Correlation between the weight of the animal and the length of the fibula (where the length of the right equals the length of the left). The results indicate that the heavier the rat, the longer its fibula.

animals used in our experiments to a more common basis, and particularly to adjust the weights in such a manner that the increase in breaking strength concomitant with an increase in weight would present less disparity when the breaking strength was plotted for each of the periodic observations made both in the normal normal group without fracture and in all other rats to be noted subsequently. In other words, our animals ranged from 190 to 300 Gm. in weight, and we had found that the heavier the animal, the stronger the fibula, but we wished to reduce all values by some formula, no matter what the weight, to a point where the great disparity in the breaking strength found on the weight range

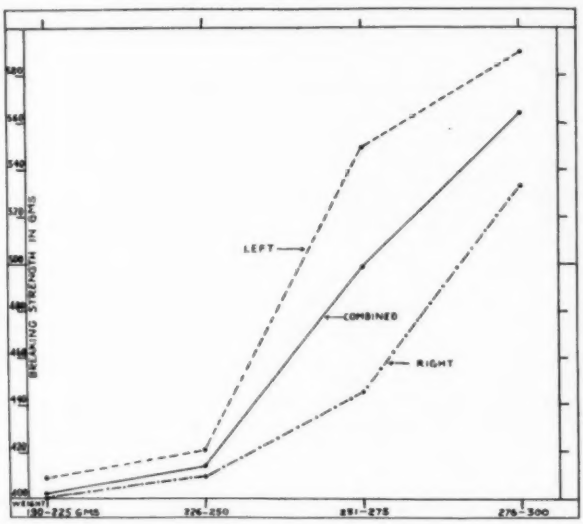

Fig. 4.—Correlation between the weight groups and mean of breaking strength of the right and left fibulae of normal normal rats, as well as correlation between the combined breaking strength means and the weight groups. It is seen that the more the animal weighs, the stronger is its fibulae.

TABLE 4.—*Correlation Between Weight and Breaking Strength* *

	Weight Groups							
	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of breaking strength...	409	394	421	410	550	446	595	533
Combined mean	401		415		498		564	

Refer to table 4a for complete data.

from 190 to 300 Gm. would be reduced, and all animals might be considered as though they were of essentially the same weight.

To develop such a formula, we reasoned as follows: It was observed in fifty determinations that the force required to break the fibulae of the

rat was positively correlated with the animal weight. Undoubtedly this was not the only source of variation, but in order partially to reduce this fluctuation, it was desired to introduce some factor J by which to divide the observed values of F, where F is the force or breaking strength, and J is some function of W, the animal weight, i. e., the normal weight before subjection to fracture and after seven days on diet. As a first approach to a satisfactory solution in this matter, we might consider that all animals used were similar in form (linear

TABLE 5.—*$W^{2/3}$ for W from 190 to 300, Inclusive* *

W	$(10.w)^{2/3}$	W	$(10.w)^{2/3}$	W	$(10.w)^{2/3}$	W	$(10.w)^{2/3}$
190	153.4	220	169.1	250	184.2	280	198.6
1	154.0	1	169.7	1	184.7	1	199.1
2	154.5	2	170.2	2	185.2	2	199.6
3	155.0	3	170.7	3	185.6	3	200.1
4	155.6	4	171.2	4	186.2	4	200.6
5	156.1	5	171.7	5	186.7	5	201.0
6	156.6	6	172.2	6	187.1	6	201.5
7	157.2	7	172.7	7	187.6	7	202.0
8	157.7	8	173.2	8	188.1	8	202.4
9	158.2	9	173.7	9	188.6	9	202.9
200	158.8	230	174.2	260	189.1	290	203.4
1	159.3	1	174.7	1	189.6	1	203.8
2	159.8	2	175.2	2	190.1	2	204.3
3	160.3	3	175.8	3	190.5	3	204.8
4	160.9	4	176.2	4	191.0	4	205.2
5	161.4	5	176.8	5	191.5	5	205.7
6	161.9	6	177.3	6	192.0	6	206.2
7	162.4	7	177.8	7	192.5	7	206.6
8	162.9	8	178.3	8	192.9	8	207.1
9	163.5	9	178.8	9	193.4	9	207.7
210	164.0	240	179.3	270	193.9	300	208.0
1	164.5	1	179.8	1	194.4		
2	165.0	2	180.3	2	194.9		
3	165.6	3	180.8	3	195.3		
4	166.1	4	181.2	4	195.8		
5	166.6	5	181.7	5	196.3		
6	167.1	6	182.2	6	196.8		
7	167.6	7	182.7	7	197.2		
8	168.1	8	183.2	8	197.7		
9	168.6	9	183.7	9	198.2		

* The result of the division of F by $(110.w)^{2/3}$ was arbitrarily multiplied by 106 in order to reduce the number of decimals, and to facilitate the charting of the results.

dimensions proportional); that breaking strength of the bone was proportional to cross-sectional area at the breaking surface, and that breaking occurs in a similar manner in all instances. If so, then if A is the ratio of a given linear measurement of a given animal to the average or any other arbitrary standard value of this measurement, then the similar ratio (magnitude factor) for the area mentioned would be A^2 and for W the corresponding factor would be $A.^3$ Now, if we take J proportional to $A,^2$ we have a solution. Accordingly,* we took

* The choice of the value $J = (10.W)^{2/3}$ may seem strange, but it was employed to coincide with results of preliminary calculations where $J = W^{2/3}$ was taken with W in decigrams.

$J = (10.W)^{\frac{2}{3}}$ or the real cube root of the square of (10.W). The formula would then be $\frac{F}{(10.W)^{2/3}} = R$ (ratio). To facilitate the determination of $(10.W)^{\frac{2}{3}}$, we have prepared table 5 for W from 190 to 300 Gm. inclusive (table 5).

With the aid of this formula, we corrected all our breaking strength determinations on the normal normal rats as may be seen in table 6.

TABLE 6.—$\frac{F}{W^{2/3}} = R$ *(Fifty Normal Normal Rats)**

	W	Weight $(10.w)^{2/3}$	F Left	F Right	R of Left	R of Right
Arithmetic mean	243	177	458	440	252	243
Standard deviation mean	...	...	20	19	9	9

* Refer to table 6a for complete data.

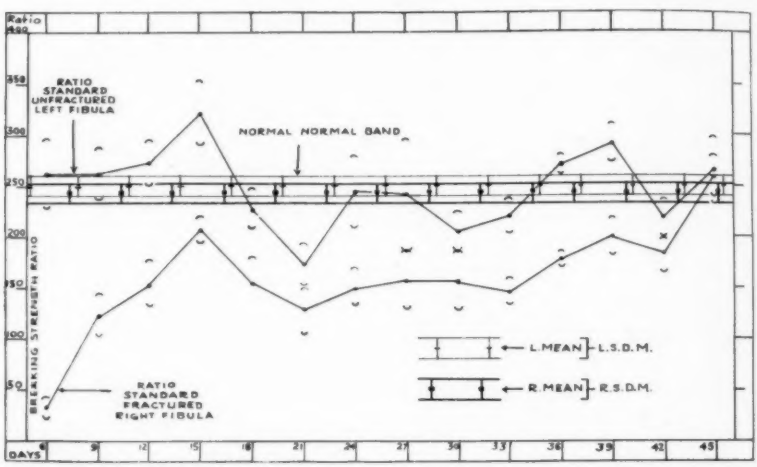

Fig. 5.—The breaking strength ratios of the normal normals and the standard groups with fractures. The straight band represents the normal normals. The mean of the left fibula is 9 greater than that of the right (L. Mean and R. Mean). The standard deviations of the mean depreciate this difference somewhat (L. S. D. M. and R. S. D. M.). The band indicates the ratios of fifty normal rats and affords a basis with which to compare ratios obtained on the different diets to be used. The primary callus has formed in the fractured right fibula by the fifteenth day. The medullary cavity develops by the twenty-first day. Thereafter strength is restored by cortical thickening and callus reorganization. Healing is theoretically complete by the forty-fifth day. The unfractured left fibula rises and falls simultaneously with the right. This may indicate a generalized skeletal response to the fracture.

When the ratios were plotted, we found a broad band passing across the chart with the left fibula stronger by a ratio of 9 than the right. However, if the standard deviations for the left and right are determined, it is observed that there is considerable overlapping of the two and that the difference is not significant (fig. 5).

The normal normal band, composing as it does the breaking strength ratio of the fifty normal animals, is considered throughout our work as representing the values on normal animals within the weight group used. In the case of healing fractured right fibulae, both of animals in the standard series with fracture and possibly of those on all diets, healing may be considered to be complete when the strength of the fracture falls within or above this band, but our work is not yet sufficiently advanced with other diets for us to be certain of this. In a similar manner, plotted variations in the strength of the unfractured left fibulae in the standard groups with fracture can be seen clearly by use of the band, and our reason for assuming that the unfractured left fibulae in the animals with fracture cannot be used to control the fractured right fibulae will become apparent when we note later the marked fluctuations to one side or the other of the band that the unfractured left fibular ratio of the standard group with fracture presents.

II. *Standard Control Group.*—The results obtained on this group of animals are of particular interest for two reasons. For one thing, the breaking strength ratio of the standard controls compared both with the ratios of the normal normals and of the standard group with fracture proved quite interesting. For another thing, the difference in the metabolic reaction of the standard control rats to that of the standard group with fracture was very clearcut. Correlations between animal weight, fibular length and fibular strength on the standard control animals were also made in a similar fashion to those drawn on the normal normals.

A. Breaking Strength: The ratios for the left and right fibula, respectively, lie, as we found in the normal normals, in close proximity. When they are considered together it is noted that they fall from around 330 on the sixth day period to a low point on the eighteenth day of approximately 175. This is followed by an abrupt rise to about 285 on the twenty-fourth day which is the highest ratio reached throughout. A fall to 150 occurs by the thirty-third day, and a rise with a slight fall thereafter follows on the forty-second and forty-fifth days, respectively. In table 7 the respective ratios with their standard deviations are recorded, while in figure 6 the ratios have been plotted.

When we compare the ratios of the breaking strength ratios of the right and left fibulae of the standard control group in figure 6 with those of the normal normals, as is plotted in figure 5, we observe that the control ratios fluctuate widely on either side of the normal normal means. Consequently, we believe that it is a justifiable assumption to state that the strength of the standard controls throughout showed a progressive loss in strength directly proportional, within limitations, to the length of time on diet. At a later point a comparison between the control and the fracture ratios will be made.

B. Correlations: In a similar manner to that observed on the normal normals, correlations between animal weight, fibular strength and fibular length were made for the standard controls. It was found that such correlations could readily be made, and that though the means differed, the progress of the curve was essentially the same.

TABLE 7.—*Breaking Strength Ratio of Right and Left Fibulae of Standard Control Group* *

Postoperative Days	Standard Deviation Mean R for Left With	Standard Deviation Mean R for Right With
6	333 ± 11	319 ± 5
9	255 ± 20	241 ± 16
12	231 ± 39	244 ± 50
15	186 ± 4	186 ± 8
18	175 ± 6	169 ± 8
21	216 ± 20	182 ± 16
24	285 ± 23	282 ± 25
27	270 ± 43	252 ± 25
30	207 ± 10	201 ± 14
33	151 ± 18	152 ± 14
36	188 ± 18	169 ± 19
39	213 ± 13	199 ± 9
42	222 ± 16	226 ± 20
45	218 ± 12	209 ± 15

* Refer to table 7a for complete data.

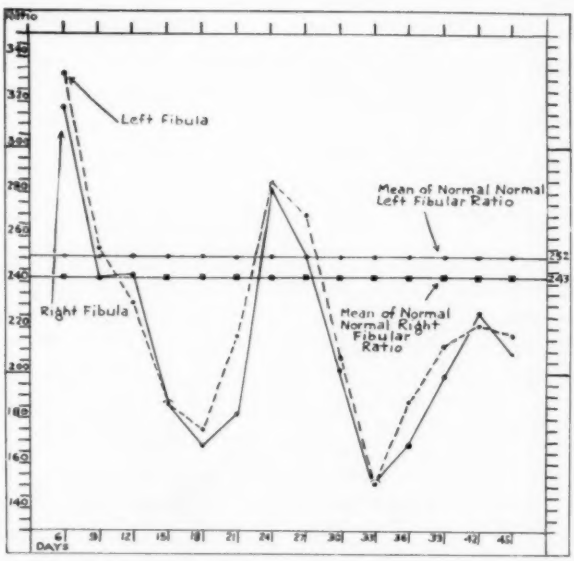

Fig. 6.—The breaking strength ratios of the standard controls without fractures compared with that of the normal normals. The relatively close agreement between the ratios of the standard right and left fibulae is seen. The somewhat irregular, but progressive loss of strength proportional to the time the animals are on diet is clearly brought out. This furnished the first lead that the normal bone strength is strongly influenced by the diet and body weight.

The weight and length were correlated as they had been in the normal normals with the results seen in table 9.

Under the normal normals, we arbitrarily divided the animals into groups according to weight. A similar division was made here, but it was found that a less striking correlation existed. This might be attributed to the small number and otherwise unsatisfactory character of animals selected in the division from 251 to 275 Gm. When this was corrected, as it was when the high fat and high carbohydrate diets

TABLE 8.—*Correlation Between Fibular Length and Strength* *

	2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of strength	308	298	317	299	400	388	536	576
Combined mean	303		308		394		520	

* Refer to table 8a for complete data.

TABLE 9.—*Correlation Between Fibular Length and Animal Weight* *

	2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.
Arithmetic mean of weight	214	223	233	278

* Refer to table 9a for complete data.

TABLE 10.—*Correlation Between Animal Weight and Fibular Strength.* *

	190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
	Left	Right	Left	Right	Left	Right	Left	Right
Arithmetic mean of strength	303	289	373	373	593	566	528	504
Combined mean	296		373		580		516	

* Refer to table 10a for complete data.

were used (to be reported later), it was found that a stronger correlation between animal weights and fibular strengths could be drawn for the control rats as well as for the normal normals.

C. Data on Food Intake and Weight of Rats: The results of the metabolic studies are not sufficiently detailed to afford conclusive observations, but their relative value has proved quite worth while for our understanding of the problem of the healing of fracture on the various diets undertaken.

In the case of the standard control animals our data have been compiled with two ends in view. The first was to determine what percentage difference in weight took place in the rats from the sixth day on the diet until they were killed which was determined by estimating the gains and losses in weight on the day of killing as percentage of body weight on the sixth day. The second end sought was to deter-

mine the food consumed per day in terms of percentage of body weight from the time of operation until the rats were killed.

When these two values were determined, it was noted that from the sixth day on there was a steady though somewhat irregular loss in the weight of the rats, as well as a slight but progressive diminution in their food intake. These observations have been recorded in table 11.

When the percentages are plotted, we note that the picture of steady loss of weight and decreased food consumption is brought more clearly to our attention. In figures 7 and 8 we have charted the percentage along with those for the standard group with fractures with which they will later be compared.

TABLE 11.—*Data on Food and Weight* *

Days	Difference in Weight From Operation to Time of Killing as per Cent of Weight on Sixth Day	Food Consumed per Day From Operation to Time of Killing as per Cent of Weight on Sixth Day
6	— 2.25	3.75
9	— 4.25	3.33
12	— 4.64	3.37
15	— 3.77	3.30
18	— 7.11	3.46
21	— 7.20	3.44
24	—15.02	3.43
27	—12.03	3.11
30	— 6.35	2.92
33	—12.76	2.93
36	—11.45	3.39
39	—11.06	2.92
42	—16.27	2.99
45	—18.39	2.82

* Refer to table 11a for complete data.

III. *Standard Fractured Group.*—These animals probably constitute the most important series of this problem. The results obtained are divided for purposes of greater clarity into several subheadings.

A. Gross Examination of the Fracture: The gross appearance of healing fractures has been repeatedly studied by other workers. However, we have observed selected fractures under the dissecting microscope from the sixth to the forty-fifth day in this group of rats. An irregular translucent and somewhat gelatinous appearing tissue was at first seen about the site of the fracture. This possessed a spindle shape and was of greater diameter about its mesial portion and fused into the shaft peripherally. By the fifteenth day the previously soft structure had become firm, granular and opaque. From the fifteenth day on there was a gradual transformation of the callus into a smooth, regular and firm structure.

When the callus was examined end on after being subjected to and broken in the beam test, a much better picture of the healing process was

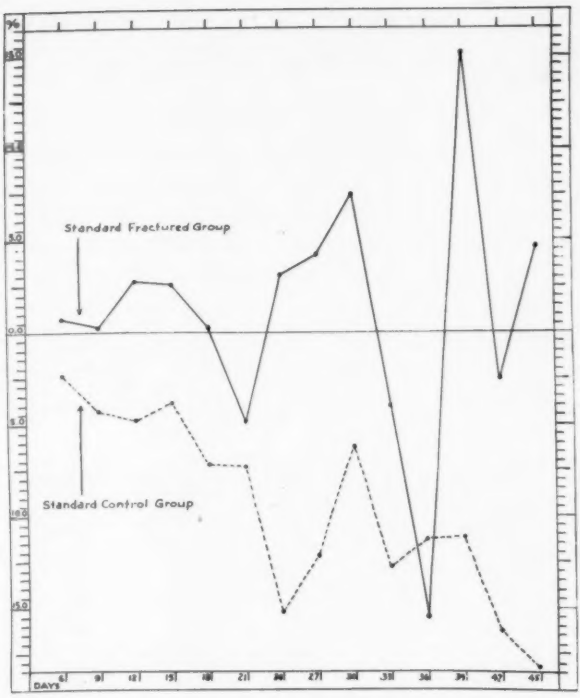

Fig. 7.—Curve showing the difference in weight from operation until the animal was killed (plotted as per cent of body weight at operation). The early stimulating effect of the injury is observed in the rats with fractures. After the formation of the primary callus on the fifteenth day, the weights of the lot with fractures fluctuated widely, but with a constant tendency to increase. The controls lost weight from start to finish. Simultaneously with falling weight, we have already seen in figure 6 that the fibular strength diminished.

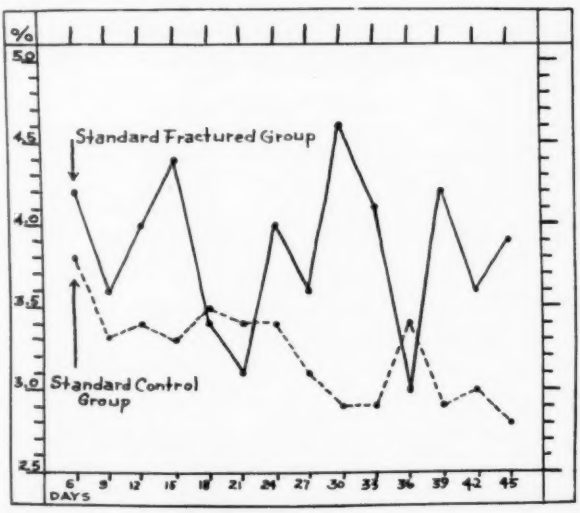

Fig. 8.—The food consumed per day (represented by curve plotted as per cent of body weight at operation) from operation until the animal was killed, for both the animals with fracture and the control series, varied considerably. This was particularly true of the rats with fracture. However, as food intake fluctuated, both body weight and fibular strength simultaneously increased or decreased.

observed. By the fifteenth day it was seen to have become entirely impregnated with salts throughout its cross-sectional area. Thereafter there grew into this solid mass of salts countless fine blood vessels which by the thirty-third day had almost entirely fused medially to form the medullary cavity. The cortex simultaneously thickened slowly, and the diameter of the callus diminished, until by the forty-fifth day the process appeared complete.

B. Diameter of the Callus: Representative calluses were measured for each observed period. The measurements, though incomplete, substantiated the opinion given by the gross examination that the diameter

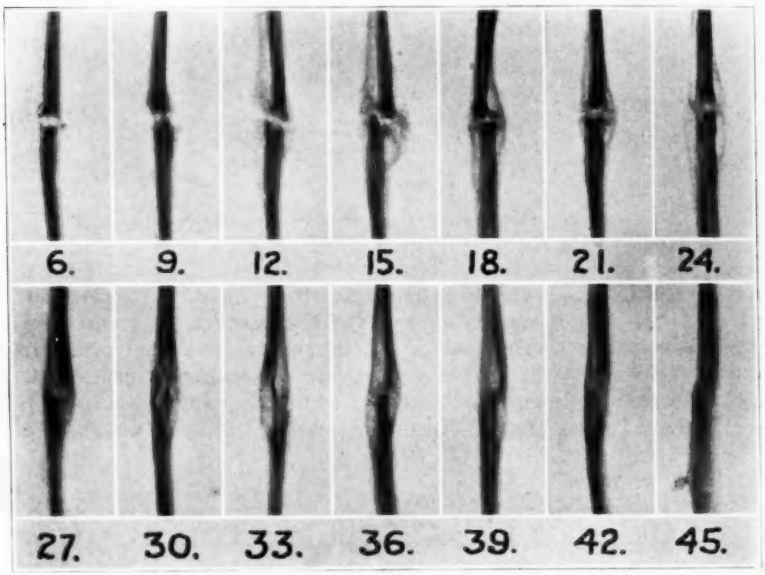

Fig. 9.—Roentgenograms of typical fractures at intervals of three days from the sixth to the forty-fifth postoperative days. The primary callus was formed by the fifteenth day. The medullary cavity is well developed on the twenty-first day. Thereafter the cortex thickened and the callus reorganized. The strength of the callus after the fifteenth day was found to bear only slight relation to the degree of density observed in the roentgen studies. Magnification, × 3.5.

increased to the fifteenth day and diminished thereafter. The diameter throughout did not, however, at any time become reduced to that of the diaphysis.

C. Roentgenographic Examination: It was observed from the roentgenographic studies for each period that the apposition of the fracture was good and angulation reduced to a minimum. From this we believe our policy of not splinting the fracture is vindicated.

From the sixth to the fifteenth day, inclusive, a progressive enlargement in the diameter of the callus was seen in the x-ray films. A similar increase in density took place with a noticeable irregularity in the salt depositions. The fractured fibular ends were seen to be undergoing decalcification simultaneously with increasing density of the callus (fig. 9).

Between the fifteenth and thirty-third days, irregularities in opacity are noted in the roentgenograms as the processes of modeling, cavitation, and formation of the medullary cavity occur. Following this, and in fact occurring simultaneously, cortical thickening and reshaping of the

TABLE 12.—*Breaking Strength Ratio of Fractured Right and Unfractured Left Fibulae* *

Day	Ratio	
	Fractured Right	Unfractured Left
6	33 ± 8	264 ± 32
9	124 ± 21	262 ± 24
12	153 ± 22	274 ± 20
15	208 ± 13	326 ± 29
18	156 ± 26	228 ± 19
21	128 ± 19	172 ± 21
24	149 ± 18	245 ± 32
27	168 ± 31	243 ± 50
30	167 ± 29	207 ± 16
33	157 ± 14	220 ± 17
36	179 ± 9	274 ± 13
39	202 ± 19	294 ± 20
42	184 ± 17	217 ± 18
45	258 ± 23	269 ± 31

* Refer to table 12a for complete data.

previously roughened, irregular callus takes place, until on the forty-fifth day a healed fibula of comparatively uniform density has developed.

D. The Breaking Strength: The breaking strength was observed on both the fractured right and the unfractured left fibulae, and, as the results obtained differ decidedly in each, they are considered separately.

1. Fractured right fibula:

All breaking strength results were expressed in terms of the ratio or R, and are so described.

There was a sharp rise in R from the sixth to the fifteenth day coincidentally with increasing salt precipitation as indicated both on gross and roentgenographic examination. R on the fifteenth day was 208 ± 13 which, as may be seen on table 12, was the highest point reached in the stage of primary callus formation (table 12).

Subsequent to the fifteenth day, an abrupt fall during the eighteenth and twenty-first day occurred, reaching a low point of 128 ± 19. This took place simultaneously with the development of the medullary cavity.

as was noted in the gross examination. Apparently there can be little doubt that the inbudding blood vessels, forming the medullary space by their fusion, weaken the callus.

From the twenty-fourth day, the breaking strength steadily rose with slight variations from time to time. This we would expect both from the roentgenograms and the gross examination, for we have previously found that as the medullary cavity developed, the cortex thickened and the callus reorganized.

By the forty-second day the ratio reached 184 ± 17, and was followed by a rapid incline to 258 ± 23 by the forty-fifth day. The rise was striking and well defined. The ratio on the forty-fifth day fell within the normal normal band passing across figure 5, and consequently was considered to be the end-point. In addition, the arithmetic means of the ratio fell within the standard deviation of the mean for the unfractured left fibula.

2. Unfractured left fibula: It becomes apparent at once when figure 5 is examined why the unfractured left fibula cannot be used as a control for the fractured right fibula. The plotted ratios for the left fibulae do not present a moderately straight line similar to that of the normal normal band, nor do they possess any of the characteristics of the unfractured left fibulae in the standard controls, as seen in figure 6. On the contrary, the left fluctuates in strength, as does the right, and surprising as it may seem, these fluctuations roughly occur simultaneously with similar increases and decreases in the healing strength ratios of the fractured right fibulae. Consequently, attempts to plot the ratios of the right in terms of percentage of the left fibulae are impossible.

The exact ratios of the left fibulae as given in table 12, and as plotted in figure 5 show these fluctuations clearly and afford a ready table of results from which to conclude that we cannot call the left normal, nor can we use it to control the right. The explanation of this is at present problematic, but possible theories will be discussed later.

E. Data on Animal Weights and Food Intakes: The metabolism of the standard groups with fracture was studied in a manner similar to that of the standard controls, and the same compilation of data was made. The data have been plotted along with that of the controls in figures 7 and 8.

The animals with fracture showed a moderate but readily identifiable gain in weight from the sixth to the fifteenth day, at which time, simultaneously with a sharp loss in the strength of the callus, the increasing weight reversed its course and fell from plus 2.6 per cent on the fifteenth day to plus 0.4 per cent on the eighteenth. By the twenty-first day the percentage had dropped to minus 4.7 per cent. The

percentage then rose to plus 7.5 per cent on the thirtieth day only to be followed by a sharp and rapid fall to minus 15.5 per cent by the thirty-sixth day. Thereafter it rose to plus 15.1 per cent on the thirty-ninth day, fell to minus 2.7 per cent on the forty-second day and rose and ended with plus 4.7 per cent on the forty-fifth day as is seen in table 13.

The interesting point of the differences in weight from operation until the animal is killed as percentage of body weight at operation lies in its correlation with the breaking strength ratios. An agreement apparently exists as shown by a rising percentage up to the fifteenth day, simultaneously with the greatest strength in the primary callus, but thereafter the correlation is hard to draw. The elevation of

TABLE 13.—*Body Weight and Food Intake* *

Day	Difference in Weight From Operation to Time of Killing as per Cent of Weight at Operation	Food Consumed per Day as per Cent of Body Weight at Operation
6	+0.9	4.2
9	+0.4	3.6
12	+2.9	4.0
15	+2.6	4.4
18	+0.4	3.4
21	—4.7	3.1
24	+3.2	4.0
27	+4.4	3.6
30	+7.5	4.6
33	—4.0	4.1
36	—15.5	3.0
39	+15.1	4.2
42	—2.7	3.6
45	+4.7	3.9

* Refer to table 13a for complete data.

metabolic percentages on the thirtieth day occurs coincidentally with the completion of the stage of modeling and the formation of the medullary cavity. However, the subsequent fall may be due to individual variations in the animals on the thirty-sixth day or to some other metabolic factors at present unknown. Likewise, the sharp rise on the thirty-ninth day to an opposite extreme from the loss on the thirty-sixth day is inexplicable. These will be discussed at a later point in this paper.

The food consumed per day observed as percentage of body weight at operation, and plotted in figure 8, agrees in a similar fashion to that found for the standard controls with the weight percentages in that with loss of weight the food consumed diminished, and concomitantly with gain in weight there was an increase in food consumption.

It is especially notable that on the fifteenth day the percentage of food consumed was 4.4 per cent at which time the primary callus was at

its greatest strength. With the loss in strength in the callus, the food consumption diminished. On the thirtieth day the percentage was at + 4.6 per cent, which was its greatest height. Table 13 gives the data for both the weight and food percentages.

COMMENT

The value of the beam testing machine for determining the healing strength of fractured fibulae of rats, as well as the normal breaking strength, appears unlimited, but actually it possesses definite limitations which will be discussed later. However, the simplicity of its mechanism and the comparative accuracy of its determinations warrant a careful consideration of the results obtained from it.

On the normal normal rats the correlations observed between fibular length, fibular strength and animal weight substantiated the findings of several previous workers, but the correlation shown to exist between the animal weight and the breaking and healing strength of the fibula proved to have an added value. Through this correlation we developed the formula $\frac{F}{(10.W)^{2/3}} = R$, by means of which we were able to discount considerably the variations in breaking strength due to the disparity in the animals' weight from 190 to 300 Gm. The band resulting from the observations on the normal normals gave us a comparative guide by means of which we could adjudge the degree of normalcy of any given determinations within similar weight and age limits.

The standard control group, being free from fractures and on the standard diet for the same interval in each period as a similar group of the standard animals with fracture, proved to be of considerable merit from two angles. In the one case it was found that the trend of the breaking strength of this group fell or diminished in direct proportion to the duration of time they were on diet. True, there was a rise of the breaking strength on the twenty-fourth day, but throughout the trend was downward. In the second instance, this group showed a steady loss of body weight and a diminution in the quantity of food consumed. Again, there were found fluctuations in the two curves presenting these results, but their course was a constantly decreasing percentage from beginning to end. The apparent correlation between loss in fibular strength and loss in animal weight may be attributable to the influence of the diet on the metabolism of the bone, especially on those metabolic factors that determine the strength of the bone.

The unfractured left fibula in the standard fractured series fluctuated in strength concomitantly with similar fluctuations in the healing strength of the fractured right fibula. As the primary callus increased in strength to attain its highest level on the fifteenth day, the strength

of the left likewise rose, and as the callus lost strength (seemingly through formation of the medullary cavity) the left also showed diminished breaking strength. Moreover, with subsequent cortical thickening and increased strength in the fracture, the strength of the unfractured left fibula also increased. At first glance one is strongly inclined to believe that this reaction presents evidence that the fracture is producing not a local response to injury, but rather a generalized skeletal reaction by means of which the skeleton fluctuates in strength as the fracture fluctuates. There seems little reason to doubt this within limitations. It is true that the unfractured left fibula may be varying in strength due to neurogenic stimuli arising in and crossing over from the fractured right fibula with consequential variations in blood supply to it, but we have found that the radii of the forelegs vary in strength also, so this cannot be the entire picture. It is also quite possible that phosphatase and the parathyroid hormone as personally suggested by Kay are factors in the rise and fall of strength in the left fibula, and this deserves special consideration.

Phosphatase is an enzyme found especially in growing bone which possesses the power to transform the organic phosphate compound to an inorganic one in which form it is found in the bone. Kay [4] determined that phosphatase exists in the circulation as well as in the growing epiphysis; in fact, in various bone diseases he recently found in some cases remarkable changes in the blood phosphatase level. In our laboratories, Ostergren and one of us (Dr. McKeown) showed in an unpublished preliminary study that the phosphatase of the rat skeleton with a fractured right fibula rises to the fifteenth day, and thereafter falls slowly back to its starting point. We saw in our gross examination of the callus, mentioned earlier in the paper, that the healing fracture became heavily impregnated with salts by the fifteenth day. In explanation of this, Harris [5] called our attention to the fact that this occurs in cartilage cells past the height of their growth curve and in the presence of an extremely small quantity of tissue fluid. He apparently would have us believe that calcification occurs in a diminished circulation of tissue juices and associated with vitamin D. Fell and Robison,[6] in cultivation in vitro of embryonic limb buds, found phosphatase formed by hypertrophic cartilage cells only. Thus, we seem to be confronted with two phases of phosphatase activity. A local response occurring

4. Kay, H. D.: Plasma Phosphatase: II. The Enzyme in Disease Particularly in Bone Disease, J. Biol. Chem. **89**:249, 1930.

5. Harris, H. A.: Cod Liver Oil and the Vitamins in Relation to Bone Growth and Rickets, Am. J. M. Sc. **181**:453 (April) 1931.

6. Fell, H. B. and Robison, Robert: The Growth, Development and Phosphatase Activity of Embryonic Avian Femora and Limb Buds Cultivated in Vitro, Biochem. J. **23**:767, 1929.

at the fracture site simultaneously with cartilage formation and leading to calcification of the callus with increasing strength therein until the fifteenth day, and a generalized skeletal reaction occurring coincidentally, which we may assume to be due either to an overflow of phosphatase from the fracture or a stimulation to increased phosphatase production occurring at all phosphatase centers in response to a substance elaborated by the fracture, and in either case resulting in greater skeletal strength from accelerated calcification. This is to no small extent hypothetic at the present time, but yet may afford a basis for future advances along this line.

The falling strength noted in both the standard fractured right and left fibula may possibly be due to parathyroid hormone. It is difficult to believe that the mere mechanical activity of osteoclasts, or the fusing of the medullary blood vessels to form the medullary cavity, could in the space of six days produce the abrupt fall in strength seen in the healing fracture. Likewise in the fractured left fibula, since we are not confronted with a developing medullary cavity, we cannot at present assume any accelerated osteoclastic activity. As in the case of increasing strength and phosphatase, we are then confronted with the fact that the falling strength must be due largely to a circulating substance, and such a decalcifying substance that would produce falling strength could conceivably be the hormone of the parathyroid glands. We may then assume that phosphatase and parathyroid hormone are antagonists in the sense that the first accelerates calcification while the second accelerates decalcification.

However, although all the foregoing assumptions are attractive, there still remain several results to consider that are not only interesting but afford a basis for very appealing speculations. It will be recalled that on the normal normals we found the more the animal weighed, the stronger was its fibula. There seems no reason why this should not be stated in the reverse order; namely, that the lighter the animal, the weaker the bone. Turning to the breaking strength of the standard controls, we see that there was a progressive loss in strength from the sixth to the forty-fifth days, and that with this diminution the weight of the rats and the food they consumed fell from the beginning to the end of the experiment. Consequently, with this decrease in food and weight, the animals became lighter, and, becoming lighter, the strength of their fibulae fell. This was an important observation, for it may go far to explain the fluctuations observed in the breaking strength of the unfractured left fibula in the standard series with fracture.

The strength of the unfractured left fibula rose on the fifteenth day, while the weight as well as the food intake had also risen by the same day. Between the fifteenth and the twenty-first days, the strength fell

and, at the same time, the body weight and the quantity of food consumed decreased also. This agreement between strength of the fibula, animal weight and the amount of food consumed exists throughout. There are sharp rises and falls, but, in general, this comparatively close relationship of one to the other is readily seen.

We know that the increasing strength in the fractured right fibula up to and including the fifteenth day is due to the formation of the primary callus. The simultaneous gain in weight throughout this interval we assume to be due to the stimulated metabolism occurring in the early reparative state that is said by workers in the field to follow any extensive tissue injury. Harvey and Howes obtained strong evidence to support this opinion in their studies on wound healing in the rat.

After the fifteenth day the healing strength of the fractured right fibula falls to the twenty-first day, only to rise again through a slow sweeping curve. The nature and the relative smoothness of the curve could be better seen if the line were to be drawn without attempting to include the arithmetical means of each periodic observation. Such a curve would then be not irregular with peaks and valleys, but rather even and regular. It would probably take the form of a sigma, and be expressive thereby of a chemical reaction. One is led to wonder if the body weights and the food intake were constant from beginning to end of the experiment, if such a curve would not be obtained.

Although we may surmise that the animal weight and the fibular strength are closely correlated, we still find ourselves at sea in respect to the mechanism that adjusts the weight to produce the variations noted in the strengths from interval to interval. There is an undoubted factor of uniformity in the influencing agent, as we can see when the fibular strengths are studied. Harris,[5] as we noted before, would have us believe that vitamin D controls calcification while vitamin A regulates the process of ossification. There seems no occasion for us to believe that the quantity of these vitamins available for absorption varies, but possibly the fracture elaborates a substance essential to the activity of the vitamins and which also influences the animals' desire for food.

To consider the roentgenograms obtained in these studies, it has been pointed out by Eliason [7] that the usefulness of the roentgenogram as an index of the degree of healing in the fracture is only during the period of primary callus formation. This was further emphasized in our studies. The roentgenogram outlined a maximum callus on the fifteenth day which agreed with the breaking strength ratio at that time,

7. Eliason, L. E.: Nelson's Loose Leaf Surgery, New York, T. Nelson & Son, 1927, vol. 3, p. 249.

but this was followed by a loss of strength which was only suggested in the roentgenogram. Thereafter, the agreement of the findings between the roentgenogram and the breaking strength became less. The rarefaction of the fragments was, however, readily seen as was the well healed fracture on the last two periods observed. The roentgenogram is of undoubted value, but considerable care must be exercised in attempts to interpret the strength of the callus from the picture seen.

The histologic studies in process of preparation on the healing fractures of animals on the different diets that we are using in our work calls for passing attention. These will be reported in a separate series of papers in the near future. An attempt will be made in these to correlate the breaking strength with the predominating cell response present on the different intervals.

SUMMARY

By use of an original beam testing machine, the breaking and healing strengths of normal and fractured fibulae of rats were studied. It was observed that:

1. The strength of the fibula of the rat was shown to be positively correlated with the fibular length and the animal weight. Similar correlations were shown to exist for any combination of these three variables.

2. The relation of body weight to fibular strength proved of considerable value. A formula to reduce the disparity in weights was developed. This resulted in the use of a breaking ratio R, as defined in the text.

3. The breaking strength of fifty pair of unfractured fibulae of normal normal rats on the standard diet one week had a ratio of 252 ± 9 for the left and 243 ± 9 for the right, respectively.

4. A series of standard control rats, free from fracture and on standard diet for from thirteen to fifty-two days, showed a breaking strength ratio which at times varied widely, but which fell steadily from the beginning to the end of the experiment.

5. There were found to exist simultaneously with the falling strength similar fluctuations in the animal weights and the quantitative food intake. As the one fell, the other fell, and as the one rose, the other likewise rose.

6. Similar correlations between animal weight, fibular length and fibular strength were seen to exist for this series of rats as for the normal normals.

7. A series of animals was kept on the standard diet for one week. Their right fibulae were then fractured. The rats were then killed at intervals of three days from the sixth to the forty-fifth days post-operatively, and the breaking strength ratios of the unfractured left fibulae and the healing strength ratios of the fractured right fibulae were determined. The ratio of the fractured right fibula rose sharply to the fifteenth day, by which time the primary callus had formed. The ratio fell from the fifteenth to the twenty-first days as the medullary cavity developed, and slowly rose by a process of cortical thickening and reorganization of the callus to equal the normal normal ratio on the forty-fifth day, when strength was considered to have been restored.

8. The ratios of the unfractured left fibulae closely followed the rises and falls in the ratios of the fractured right fibulae.

9. Again the animal weights and food intakes varied simultaneously with differences in the ratio from interval to interval.

10. Roentgenograms followed the healing strength ratios until the fifteenth day, after which the degree of density seen proved to be no indication of the true strength of the healing fibula.

11. The explanation of the comparatively close agreement between fluctuations in breaking or healing strength and animal weight and food intake is problematic. Several possibilities were considered, especially vitamins A and D, phosphatase, parathyroid hormone and the elaboration of a chemical substance at the fracture site.

CONCLUSIONS

1. The breaking strength ratio of the normal left fibula of the adult rat is 252 ± 9, and of the right fibula 243 ± 9.

2. A close correlation exists between body weight, fibular length and fibular strength in normal rats.

3. Normal fibular strength diminishes in rough proportion to the time the animal is on the standard diet (Moise and Smith).

4. The healing strength ratio of fractured right fibula of the rat rises with the formation of the primary callus, and falls with the development of the medullary cavity. Strength is restored to normal by the forty-fifth day through cortical thickening and reorganization of the callus.

5. Changes in the quantity of food consumed and the rats' weight exert a strong influence on both the healing and the normal breaking strength of the fibulae.

6. The roentgenogram is of distinct value in determining the fracture strength only up to the formation of the primary callus. Thereafter its value diminishes.

ADDENDA

COMPLETE DATA FOR STANDARD DIET

TABLE 2a.—*Correlation Between Fibular Length and Fibular Strength in Normal Normal Rats*

2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.	
Left	Right	Left	Right	Left	Right	Left	Right
535	380	610	515	700	675	585	605
525	370	600	620	535	480	770	800
650	460	350	325	460	505	580	465
560	480	320	350	490	445	465	700
610	555	325	360	510	495	655	565
190	205	455	435	525	510	550	620
280	340	370	600	380	375	675	410
360	300	385	400	365	360	390	380
315	320	480	515	400	435	305	360
410	290	595	500	455	385	310	400
265	400	540	660	280	360	675	335
330	300	325	375	420	420	320	305
310	250	380	310				
Mean..... 411	358	441	459	460	454	523	495
Mean of left and right combined	384		450		457		509

TABLE 3a.—*Correlation Between Fibular Length and Animal Weight in Normal Normal Rats*

2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.
236	250	290	300
234	250	284	300
216	240	282	294
212	242	273	290
210	240	263	290
210	238	252	290
210	232	246	286
203	230	235	286
202	220	228	280
201	220	224	278
200	200	200	272
195	200	240	238
192	230		
Mean 209	230	251	284

TABLE 4a.—*Correlation Between Weight and Breaking Strength of Fibulae of Normal Normal Rats*

190-225 Gm.		226-250 Gm.		251-275 Gm.		276-300 Gm.	
Left	Right	Left	Right	Left	Right	Left	Right
310	300	400	435	525	510	310	400
330	400	380	310	510	495	305	360
265	290	385	400	675	335	460	505
280	360	370	600	490	445	535	480
325	375	525	370			390	380
540	660	365	360			675	410
410	320	535	380			550	620
315	300	320	305			655	565
360	340	455	435			465	700
610	555	325	360			700	675
280	250	420	420			580	465
190	205	350	325			585	605
560	480	320	350			770	800
650	460	380	375				
595	500	600	620				
480	515	610	515				
455	385						
Mean..... 409	394	421	410	550	446	595	583
Combined mean	401		415		498		564

TABLE 6a.— $\frac{F}{10W^{2/3}} = R$ *for Normal Rats Free from Fractures on Standard Diet*

Rat No.	W	$(10.w)^{2/3}$	F Left	F Right	R Left	R Right
2547	192	155	310	300	201	194
2274	195	156	330	400	211	256
2544	200	159	265	290	167	183
2263	200	159	280	360	176	227
2288	200	159	325	375	205	236
2265	200	159	540	660	340	416
2271	201	159	410	320	257	201
2548	202	160	315	300	197	188
2284	203	160	360	340	225	212
2257	210	164	610	555	372	338
2545	210	164	280	250	171	152
2546	210	164	190	205	116	125
2294	212	165	560	480	339	291
2252	216	167	650	460	389	275
2264	220	169	595	500	352	296
2270	220	169	480	515	284	305
2251	224	171	455	385	266	225
2281	228	173	400	435	231	251
2280	230	174	380	310	218	178
2551	230	174	385	400	221	230
2277	232	175	370	600	211	342
2276	234	176	525	370	298	210
2249	235	177	365	360	206	203
2262	236	177	535	380	302	214
2277	238	178	320	305	179	171
2275	238	178	455	435	255	244
2543	240	179	325	360	181	201
2278	240	179	420	420	234	234
2280	240	179	350	325	195	181
2285	242	180	320	350	177	194
2278	246	182	380	375	209	206
2282	250	184	600	620	326	337
2279	250	184	610	515	331	280
2247	252	185	525	510	283	275
2248	263	191	510	495	268	260
2250	272	195	675	335	346	172
2267	273	195	490	445	251	228
2287	278	198	310	400	157	202
2550	280	199	305	360	154	181
2270	282	200	460	505	203	253
2268	284	201	535	480	267	239
2260	286	202	390	380	194	189
2292	286	202	675	410	335	203
2272	290	203	550	620	270	305
2261	290	203	655	565	322	278
2255	290	203	465	700	229	344
2253	290	203	700	675	344	332
2296	294	205	580	465	283	227
2542	300	208	585	605	281	291
2549	300	208	770	800	370	385
Mean	243	177	458	440	252	243
Standard deviation mean	...	...	20	19	9	9

TABLE 7a.—*Ratios of Breaking Strength of Right and Left Fibulae of Standard Control Group*

Postoperative Days	Rat No.	W	$(10.w)^{2/3}$	F for Left	F for Right	R for Left	R for Right
6	2737	262	190.1	650	625	341.9	328.7
	2475	285	205.7	670	675	325.7	328.1
	2738	265	191.5	575	590	300.2	308.1
	2739	254	186.2	675	580	362.5	311.4
						333 ± 11	319 ± 5
9	2389	300	208.0	525	575	252.4	276.4
	2390	300	208.0	470	560	226.0	269.2
	2391	284	200.6	640	440	319.0	219.3
	2415	244	181.2	400	360	220.7	198.6
						255 ± 20	241 ± 16
12	2424	220	169.1	250	220	147.8	130.1
	2425	228	173.2	290	285	167.4	164.5
	2747	250	184.2	490	560	266.0	304.0
	2748	250	184.2	630	690	342.0	374.5
						231 ± 39	244 ± 50
15	2420	210	164.0	280	265	170.7	161.5
	2421	216	167.1	320	340	191.5	203 4
	2742	198	157.7	295	300	187.1	190.2
	2423	225	171.7	330	325	192.1	189.2
						186 ± 4	186 ± 8
18	2743	194	155.6	300	260	192.8	167.1
	2417	196	156.6	275	285	175.6	182.0
	2418	230	174.2	300	320	172.2	183.7
	2419	232	175.2	280	250	159.3	142.7
						175 ± 6	169 ± 8
21	2428	295	205.7	495	380	240.6	184.7
	2429	216	167.1	260	255	155.5	152.6
	2430	210	164.0	340	260	207.3	158.5
	2431	280	198.6	515	460	258.8	231.6
						216 ± 20	182 ± 16
24	2385	290	203.4	655	625	322.0	307.2
	2386	280	198.6	630	675	317.9	339.8
	2387	220	169.1	350	350	206.9	206.9
	2388	300	208.0	605	570	290.8	274.0
						285 ± 23	282 ± 25
27	2381	235	176.8	410	380	231.9	214.9
	2382	210	164.0	310	300	189.0	182.9
	2383	260	189.1	790	775	417.7	409.8
	2744	260	189.1	450	375	238.5	198.3
						270 ± 43	252 ± 46
30	2377	238	178.3	320	305	179.4	171.0
	2378	240	179.3	420	420	234.4	234.4
	2379	236	177.3	345	390	194.5	220.0
	2380	230	174.2	380	310	218.1	177.9
						207 ± 10	201 ± 14
33	2373	225	171.7	200	225	116.4	131.0
	2374	208	162.9	320	310	196.4	190.2
	2375	210	164.0	185	200	112.7	121.9
	2376	296	206.2	365	340	177.0	164.9
						151 ± 18	152 ± 14
36	2369	267	192.5	275	260	142.8	132.4
	2476	232	175.2	425	400	242.5	228.3
	2371	207	162.4	300	280	184.7	172.4
	2372	200	158.8	285	225	179.4	141.6
						188 ± 18	169 ± 19
39	2365	222	170.2	315	280	185.0	170.3
	2366	292	204.3	440	400	215.3	195.8
	2367	212	165.0	380	350	230.0	212.0
	2368	285	201.0	445	440	221.4	218.9
						213 ± 13	199 ± 9
42	2361	245	181.7	365	390	200.8	214.7
	2362	220	169.1	325	290	192.2	171.5
	2363	300	208.0	575	590	276.4	283.6
	2364	232	175.2	385	410	219.8	234.0
						222 ± 16	226 ± 20
45	2340	235	176.8	500	475	282.8	268.6
	2341	300	208.0	505	485	242.8	233.1
	2342	230	174.2	225	220	129.1	126.0
	2458	300	208.0	505	485	242.8	233.1
						218 ± 12	209 ± 15

TABLE 8a.—*Correlation Between Fibular Length and Strength in Standard Control Group*

2 Cm.		2.1 Cm.		2.2 Cm.		2.3 Cm.		2.4 Cm.	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
275	285	300	260	300	280	320	305	445	440
280	265	295	300	320	310	630	690	440	400
340	260	285	225	325	290	490	560	470	560
185	200	370	325	200	225	790	775	525	575
380	350	310	300	425	400	575	590		
320	340	260	255	325	350	275	260		
315	280	250	220	385	410	515	460		
350	350	375	360	410	380	630	675		
300	320	300	330	420	420	640	440		
330	325	290	285	365	390	670	675		
		225	220	675	580	655	625		
		500	475	650	625	385	350		
		380	310			495	380		
		290	255			365	340		
		280	250			505	485		
		345	390			575	590		
		400	360			605	570		
		245	260						
Mean 308	298	317	299	400	388	536	516	470	494
Combined mean	303		308		394		526		482

TABLE 9a.—*Correlation Between Fibular Length and Animal Weight in the Standard Control Group*

2 Cm.	2.1 Cm.	2.2 Cm.	2.3 Cm.	2.4 Cm.
195	194	207	238	286
210	198	208	250	292
210	200	222	250	300
210	206	225	260	300
214	210	232	265	
216	216	232	267	
218	220	232	280	
220	222	235	280	
222	225	240	284	
225	228	245	285	
	230	254	290	
	235	262	290	
	230		295	
	230		296	
	232		300	
	236		300	
	244		300	
	250			
Mean 214	223	233	278	295

TABLE 10a.—*Correlation Between Animal Weight and Fibular Strength in the Standard Control Group*

190–225 Gm.		226–250 Gm.		251–275 Gm.		276–300 Gm.	
Left	Right	Left	Right	Left	Right	Left	Right
275	285	320	305	790	775	515	460
280	265	630	690	575	590	630	675
340	260	490	560	275	260	640	440
185	200	290	285	675	580	670	675
380	350	225	220	650	625	655	625
320	340	500	475			385	350
315	280	380	310			495	380
350	350	290	255			365	340
300	320	280	250			505	485
330	325	345	390			575	590
300	280	400	360			605	570
320	310	245	260			445	440
325	290	425	400			440	400
200	225	325	350			470	560
300	260	385	410			525	575
295	300	410	380				
285	225	420	420				
370	325	365	390				
310	300						
260	255						
250	220						
375	360						
300	330						
Mean 303	289	373	373	593	566	528	504
Combined mean	296		373		580		516

TABLE 11a.—*Data on Weight and Food in Standard Control Gro*

Postoperative Days	Rat No.	Weight			Food Consumed		
		Start	Operation	Death	Start to Operation	Operation to Death	
6	2475	275	285	276	90	80	
	2737	260	262	254	65	44	
	2738	260	265	258	71	47	
	2739	258	254	255	70	67	
			267	261	74	60	−6
9	2390	295	300	315	70	111	
	2391	272	284	280	50	78	
	2415	236	244	250	86	65	
	2389	300	300	330	105	122	
			282	294	78	94	+12
12	2424	220	220	226	101	67	
	2425	212	228	228	107	80	
	2747	260	250	230	49	86	
	2748	258	250	220	72	150	
			237	226	82	96	−11
15	2420	215	210	200	79	100	
	2421	212	216	210	88	94	
	2423	220	225	218	80	88	
	2742	210	198	186	48	138	
			212	204	74	105	−8
18	2417	196	195	195	76	141	
	2418	230	222	194	80	166	
	2419	232	232	225	70	156	
	2743	198	194	170	50	161	
			211	196	69	131	−15
21	2428	290	295	276	74	214	
	2429	215	216	178	56	176	
	2430	200	210	210	85	129	
	2431	270	280	262	82	202	
			250	232	74	180	−18
24	2385	280	260	220	112	228	
	2386	272	280	240	67	230	
	2387	210	220	210	67	200	
	2388	300	300	258	77	233	
			273	232	81	223	−41
27	2381	235	235	230	65	182	
	2382	210	210	192	67	199	
	2383	250	260	238	70	235	
	2744	260	260	186	59	194	
			241	212	65	203	−29
30	2377	245	238	225	57	202	
	2378	225	240	222	73	224	
	2379	230	236	218	57	160	
	2380	225	230	220	52	238	
			236	221	60	206	−15
33	2373	225	225	190	58	214	
	2374	220	208	208	54	226	
	2375	210	210	160	45	170	
	2376	285	296	260	95	307	
			235	205	63	229	−30
36	2476	230	232	200	80	355	
	2369	268	267	218	78	236	
	2371	206	207	190	52	273	
	2372	196	200	196	54	241	
			227	201	66	276	−26
39	2365	210	218	194	69	270	
	2366	204	202	248	86	309	
	2367	214	214	206	64	257	
	2368	286	286	250	80	322	
			253	225	75	290	−28
42	2361	255	245	208	58	310	
	2362	220	222	180	53	276	
	2363	300	300	234	94	371	
	2364	235	232	220	63	298	
			252	211	67	314	−41
45	2340	245	235	198	83	314	
	2341	300	300	226	93	363	
	2342	215	230	199	83	288	
			255	208	86	322	−47

TABLE 11a.—*Data on Weight and Food in Standard Control Group—Continued (Summary)*

Post-operative Days	Weight at Operation, Gm.	Difference in Weight From Operation to Death, Gm.	Food Consumed per Day From Operation to Death, Gm.	Difference in Weight From Operation to Death as per Cent of Weight at Operation	Food Consumed From Operation to Death per Day as per Cent of Weight at Operation
6	267	— 6	10.0	— 2.25	3.75
9	282	—12	10.4	— 4.25	3.33
12	237	—11	8.0	— 4.64	3.37
15	212	— 8	7.0	— 3.77	3.30
18	211	—15	7.3	— 7.11	3.46
21	250	—18	8.6	— 7.20	3.44
24	273	—41	9.2	—15.02	3.43
27	241	—29	7.5	—12.03	3.11
30	236	—15	6.9	— 6.35	2.92
33	235	—30	6.9	—12.76	2.93
36	227	—26	7.7	—11.45	3.39
39	253	—28	7.4	—11.06	2.92
42	252	—41	7.5	—16.27	2.99
45	255	—47	7.2	—18.39	2.82

TABLE 12a.—*Breaking Strength Ratios in Standard Group with Fracture*

Post-operative Days	Rat No.	Weight (W)		Force (F)		Ratio (R)	
		At Operation	$(10.w)^{2/3}$	Left	Right	Left	Right
6	2299	196	156.6	260	55	166	35
	2300	232	175.2	310	0	177	0
	2302	220	169.1	305	40	180	24
	2343	280	198.6	440	0	222	0
	2344	237	177.8	340	75	191	42
		250	184.2	750	80	407	43
		226	172.2	730	140	424	81
		220	169.1	590	50	349	30
		230	174.2	460	75	264	43
	Arithmetic mean					264	33
	Standard deviation mean					±32	±8
9	2313	255	186.7	600	415	321	222
	2316	244	181.2	670	170	370	94
	2317	238	178.3	510	340	286	191
	2318	225	171.7	610	340	355	198
	2326	243	180.8	435	185	241	102
		215	166.6	243	55	146	33
		295	205.7	465	80	226	39
		190	153.4	280	195	183	127
		205	161.4	370	170	229	105
	Arithmetic mean					262	124
	Standard deviation mean					±24	±21
12	2241	222	170.2	405	395	238	232
	2242	264	191.0	710	430	372	225
	2243	290	203.4	650	400	320	197
	2244	250	184.2	480	405	261	220
	2245	225	171.7	355	100	207	58
		268	192.9	720	390	373	202
		270	193.9	580	275	299	142
		200	158.8	330	210	208	132
		255	186.7	470	110	252	59
		213	165.6	345	110	208	66
	Arithmetic mean					274	153
	Standard deviation mean					±20	±22
15	2233	264	191.0	540	355	283	186
	2234	280	198.6	600	445	302	224
	2235	276	196.8	605	375	307	191
	2236	285	201.0	550	395	274	192
	2239	290	203.4	560	555	275	273
		200	158.8	540	360	340	227
		275	196.3	980	320	500	163
	Arithmetic mean					326	208
	Standard deviation mean					±29	±13

TABLE 12a.—*Breaking Strength Ratios in Standard Group with Fracture —Continued*

Post-operative Days	Rat No.	Weight (W) At Operation	Weight (W) $(10.w)^{2/3}$	Force (F) Left	Force (F) Right	Ratio (R) Left	Ratio (R) Right
18	2228	289	202.9	340	330	168	163
	2229	300	208.0	540	105	260	51
	2230	300	208.0	450	410	216	197
		222	170.2	310	280	182	165
		263	190.5	610	510	320	268
		195	156.1	310	275	198	183
		230	174.2	425	115	250	66
	Arithmetic mean					228	156
	Standard deviation mean					±19	±26
21	2541	300	208.0	650	295	313	142
	2539	290	203.4	265	170	130	84
	2537	273	195.3	195	375	100	192
	2534	240	179.3	405	400	226	223
	2538	285	201.0	340	180	169	90
	2540	290	203.4	300	325	147	160
	2535	190	153.4	250	115	163	75
	2536	192	154.5	200	90	129	58
	Arithmetic mean					172	128
	Standard deviation mean					±21	±19
24	2145	300	208.0	570	70	274	33
	2147	265	191.5	240	150	125	78
		300	208.0	485	390	233	188
		225	171.7	240	260	140	152
		212	165.0	295	250	179	152
		235	176.8	555	260	314	147
		300	208.0	890	415	428	200
		232	175.0	310	320	177	183
		200	159.0	530	325	334	205
	Arithmetic mean					245	149
	Standard deviation mean					±32	±18
27	2136	284	200.6	410	180	204	90
	2140	218	168.1	325	300	193	178
		215	166.6	285	140	171	84
		220	169.1	385	325	228	192
		196	156.6	225	230	144	147
		224	171.2	880	540	515	315
	Arithmetic mean					243	168
	Standard deviation mean					±50	±31
30	2127	220	169.1	315	190	186	113
	2128	210	164.0	275	160	168	98
	2130	285	201.0	425	395	212	197
	2131	230	174.2	215	...	123	...
	2133	278	197.7	425	220	215	111
		220	169.1	355	425	210	251
		258	188.1	490	560	261	298
		215	166.6	465	165	279	99
	Arithmetic mean					207	167
	Standard deviation mean					±16	±29
33	....	240	179.3	425	300	237	167
		272	194.9	440	...	226	...
		215	166.6	290	210	174	126
		275	196.3	390	400	198	204
		220	169.1	310	...	183	...
		255	186.7	330	210	177	112
		300	208.0	690	290	332	139
		250	184.2	435	360	236	195
	Arithmetic mean					220	157
	Standard deviation mean					±17	±14
36	2478	260	189.1	615	330	325	174
	2479	275	196.3	565	375	287	191
	2480	285	201.0	495	425	246	211
	2481	300	208.0	535	330	257	159
	2482	263	190.5	485	305	255	160
	Arithmetic mean					274	179
	Standard deviation mean					±13	±9

TABLE 12a.—*Breaking Strength Ratios in Standard Group with Fracture —Continued*

Post-operative Days	Rat No.	Weight (W) At Operation	Weight (W) $(10.w)^{2/3}$	Force (F) Left	Force (F) Right	Ratio (R) Left	Ratio (R) Right
39	2109	265	191.5	415	250	217	131
		210	164.0	445	280	271	171
		274	195.8	740	395	327	201
		218	168.1	480	270	286	161
		254	186.2	660	390	354	210
		200	158.8	370	435	233	273
		204	160.9	600	425	373	264
	Arithmetic mean					294	202
	Standard deviation mean					±20	±19
42	2099	250	184.2	360	385	196	209
	2104	224	171.2	340	190	199	111
		202	159.8	460	330	288	207
		218	168.1	300	330	174	196
		205	161.4	370	320	230	198
	Arithmetic mean					217	184
	Standard deviation mean					±18	±17
45	2093	200	158.8	385	350	242	220
	2094	220	169.1	480	575	284	340
	2097	229	173.7	340	275	191	158
		260	189.1	415	440	219	233
		190	153.4	295	425	192	277
		224	171.2	380	370	222	216
		235	176.8	815	650	461	368
		230	174.2	590	440	339	253
	Arithmetic mean					269	258
	Standard deviation mean					±31	±23

TABLE 13a.—*Body Weight and Food Intake of Rats in the Combined Group with Fracture*

Post-operative Days	Rat No.	Body Weight Start	Body Weight Operation	Body Weight Death	Food Consumed Start to Operation	Food Consumed Operation to Death
6	2299	200	196	190	60	37
	2300	232	232	226	57	38
	2302	210	220	225	90	57
	2343	280	280	275	63	41
	2344	227	237	235	74	48
		...	250	268	..	85
		...	226	232	..	62
		...	220	225	..	73
		...	230	230	..	87
Mean		230	232	234	69	59
9	2313	278	255	284	72	113
	2316	268	244	235	24	49
	2317	255	238	212	56	52
	2318	252	225	240	50	124
	2326	218	242	255	68	106
		...	215	220	..	49
		...	295	290	..	70
		...	190	190	..	69
		...	205	190	..	50
Mean		254	234	235	54	76
12	2241	228	222	224	62	95
	2242	265	264	289	65	174
	2243	285	290	292	71	114
	2244	265	250	261	60	113
	2245	222	225	212	72	81
		...	268	280	..	150
		...	270	298	..	132
		...	200	210	..	90
		...	255	262	..	125
		...	213	205	..	93
Mean		253	246	253	66	117

TABLE 13a.—*Body Weight and Food Intake of Rats in the Combined Group with Fracture—Continued*

Post-operative Days	Rat No.	Body Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
15	2233	268	264	285	76	152
	2234	278	280	280	139	256
	2235	270	276	260	106	144
	2236	278	285	294	84	227
	2239	288	290	296	129	155
		...	200	220	...	138
		...	275	280	...	158
Mean		276	267	274	107	176
18	2228	288	289	310	85	170
	2229	285	300	298	96	226
	2230	292	300	265	85	121
		...	222	250	..	149
		...	263	280	..	150
		...	195	192	..	132
		...	230	230	..	119
Mean		288	257	258	89	158
21	2584	245	240	240	55	160
	2585	195	190	196	20	123
	2586	212	192	190	35	165
	2587	275	273	250	61	184
	2588	280	285	275	85	156
	2589	278	290	265	90	210
	2540	280	290	265	86	175
	2541	288	300	258	76	142
Mean		257	258	246	64	167
24	2145	292	300	288	92	308
	2147	245	265	270	85	231
		...	235	268	..	276
		...	232	248	..	270
		...	200	252	..	300
		...	300	362	..	300
		...	225	180	..	164
		...	212	170	..	145
		...	300	305	..	195
Mean		269	252	260	89	241
27	2136	275	284	275	104	255
	2140	212	218	215	131	227
		..	215	210	...	178
		...	220	255	...	232
		...	196	190	...	141
		...	224	268	...	283
Mean		244	226	236	118	219
30	2127	222	220	215	78	305
	2128	202	210	204	105	285
	2130	270	285	266	96	321
	2131	222	230	218	130	323
	2133	260	278	285	100	338
		...	220	278	...	358
		...	215	280	...	372
		...	258	318	...	360
Mean		235	240	258	103	333
33	2113	230	240	225	96	344
	2116	246	272	235	95	397
	2117	215	215	190	62	265
	2118	255	275	245	95	435
	2119	200	220	193	93	357
		...	255	268	..	264
		...	250	280	..	368
		...	300	308	..	281
Mean		229	253	243	88	339
36	2478	250	260	225	68	272
	2479	270	275	230	74	251
	2480	290	285	225	60	234
	2481	290	300	270	84	351
	2482	260	263	220	84	350
Mean		272	277	234	74	292

TABLE 13a.—*Body Weight and Food Intake of Rats in the Combined Group with Fracture—Continued*

Post-operative Days	Rat No.	Body Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
39	2109	256	265	252	95	359
		...	270	240	..	341
		...	274	289	..	372
		...	218	235	..	306
		...	254	300	..	417
		...	260	285	..	390
		...	204	270	..	466
Mean		256	232	267	95	377
42	2099	230	270	226	83	367
	2104	218	224	190	85	351
		...	202	230	..	303
		...	218	225	..	333
		...	205	200	..	299
Mean		224	220	214	84	331
45	2093	205	200	196	56	369
	2094	200	220	226	73	419
	2097	200	229	196	106	336
		...	260	290	...	405
		...	190	208	...	357
		...	224	231	...	313
		...	235	290	...	356
		...	230	232	...	379
Mean		202	224	234	78	392

FRACTURES OF THE LOWER RADIAL EPIPHYSIS *

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In 1898, J. Poland very completely and thoroughly discussed traumatic separations of the lower radial epiphyses. Eight years later two masterly treatises dealing entirely with injuries to the lower radial epiphysis appeared in the Paris Theses: one by Metenier and the other by Bonta. Not until 1922 and 1924, with the reports of M. K. Smith, does this subject again attract attention in the literature.

ANATOMY

The lesion dealt with here is one in which there is a solution of continuity in the radius at its lower extremity, and all, or at least part, of the line of separation passes through the cartilaginous plate of the epiphysis. The resultant condition fulfils the requirements of, and should be called, a fracture instead of a separation or dislocation.

One knows that the longitudinal growth of a long bone is due to a proliferation of the tissue at and adjoining the epiphyseal cartilage, and the proliferating cartilaginous cells depend for their activity on their blood supply. The epiphysis obtains its blood supply from the periosteal network of arteries, large branches of which perforate the thin layer of compact tissue on its exterior and are distributed throughout the spongy cancellous tissue. Nearly the whole of the blood supply is therefore independent of the diaphysis. Only one or two minute arteries pass from the diaphysis through the conjugal cartilage into the epiphysis. This accounts for the comparatively infrequent occurrence of necrosis of the epiphysis in traumatic separation of the epiphysis even when the diaphysis is more or less completely displaced from the epiphysis. The periosteum covering the diaphysis is less adherent than that covering the epiphysis and is more easily stripped up as a result of trauma. The epiphysis toward which the nutrient artery points usually unites to the shaft first, and consequently the greater longitudinal growth is produced by the opposite epiphysis. The lower radial and ulnar epiphyses unite later than the upper ones do, and so produce the greater longitudinal growth. The synovial pouch of the carpus is in contact with the lower radial epiphysis only on its medial surface, and is rarely lacerated in fractures of the epiphysis. There are no important muscular or fibrous attachments to the lower radial epiphysis.

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* From the Fifth Avenue Hospital.

In the common posterior displacement noted in lower radial epiphyseal fractures, the following changes in the normal anatomy are noted:

1. The periosteum is torn through on the anterior aspect at the level of the conjugal cartilage and stripped up on the dorsal aspect.
2. The line of separation is smooth. There are no spicules of bone to interlock and hold the fragments separated.
3. A few fibers of the pronator quadratus muscle are lacerated.
4. Cases of radial or median nerve involvement have been reported.
5. The cells of the cartilaginous plate are more or less damaged.
6. The periosteal and nutrient artery blood supply is interfered with.

S. L. Haas, in his work on epiphyseal transplantation, stated that the epiphysis was a highly specialized tissue very much dependent on its blood supply and, for this reason, a very vulnerable tissue with its viability after transplantation directly dependent on its blood supply.

Age at Which Epiphyseal Ossification Occurs in the Lower Radius and Ulna *

		Radius		Ulna	
		Proximal	Distal	Proximal	Distal
1911	Byree	17-19	18-20	17-19	18-20
1912	Dixon	18	21-25	17	20
1911	Dwight	16	19-20	16	18
1892	Gegenbaur	17	20	17	20
1871	Henle	16	19-20	15-16	20
1909	Krause	16-17	20-21	16-17	20-21
1918	Lewis	17-18	20	16	20
1911	Poirier	16-19	20-25	20-21	22-24
1921	Terry	17	20	16-17	18-20
1921	Testal	16-20	20-25	16-20	20-25
1921	Thompson	18-20	20-25	16	20-23
Earliest		16	18	15	18
Latest		20	25	21	25
Difference		4	7	6	7

* From Stevenson (Am. J. Phys. Anthropol., January-March, 1924, vol. 7, no. 1).

The age at which epiphyseal ossification takes place in the lower radius and ulna has been variously reported. The accompanying table by Stevenson gives the ages and the authority from which each is quoted. The average is 18 years for the head of the radius, from 16 to 17 years for the head of the ulna, and 19 years for both distal epiphyses.

INCIDENCE

Fracture of the lower radial epiphysis is the most common of all the epiphyseal fractures, and, according to Poland, this frequency is due in all probability to the following facts: (1) its anatomic characteristics (it is large in comparison with its adjacent diaphysis and

it has a superficial location); (2) its skeletal situation is such that it is subject to indirect violence through trauma to the carpus and hand; (3) the lower radial epiphysis does not diminish in size in relation to the rest of the growing bone as do the epiphyses of other long bones; (4) this epiphysis is one of the last to become ossified to its diaphysis, and so it is potentially exposed to the possibility of fracture over a longer period of time, and (5) it is possible that because of its superficial location the diagnosis is less often missed than is the case with epiphyses in less accessible locations.

In 1878 Bruns reported a series of eighty-one cases with 101 fractures at or near the epiphysis, and the most frequent site was the lower end of the femur (twenty-eight cases) and next the lower end of the radius (twenty-five cases). However, his work was recorded before the use of x-rays for diagnosis. Later reports show that the lower radial epiphysis is most frequently fractured.

Age.—It is well known that the majority of cases are seen in the second decade of life. Poland gives a series of twenty-eight cases, and twenty-three of these patients were between the ages of 12 and 18. There were five patients under 9 years of age, one of these an infant aged 1 year. M. K. Smith reported twelve cases in patients with an average age of 14 years. The injury is relatively uncommon after 18 years of age.

In 1834, Dupuytren first pointed out that when a child fell on the outstretched hand, a fracture of the forearm resulted and not a fracture of the lower end of the radius as in an adult. Coulon, in his work, "Fractures in Children," made the same statement, adding that when an epiphyseal fracture does occur, it is usually in children 13 or 14 years of age and rarely before the age of 10 years. The epiphysis is relatively more resistant to trauma than the lower end of the radius in adult life. The majority of the patients are of the male sex; 80 per cent of Poland's cases were in boys.

ETIOLOGY AND TREATMENT

Etiology.—A back thrust from a fall on the outstretched hand or from hyperextension, as from a back-firing motor, are the usual causes, or, as Cotton said, the causes are the same as those which produce a Colles' type of fracture in the adult; he added that they occur more often in grown boys than in small children. These fractures are nearly always due to indirect violence, as in falls from a height on an outstretched and pronated hand when the weight of the body is transmitted through the ball of the thumb to the posterior part of the radial epiphysis, causing the fracture and the backward displacement of the lower fragment, as is most commonly the case. A direct crush-

ing blow at the site of the epiphysis may readily produce the fracture, but is an uncommon cause.

Diagnosis.—The displacement of the lower radial epiphysis is usually upward and backward. It is diagnosed by the resulting dinner-fork deformity together with increased anteroposterior diameter, limitation of flexion and extension, and radial deviation; also by pain and point tenderness on pressure over the epiphyseal line. Impaction is rare. Roentgenograms of the normal as well as the injured wrist should be taken in the anteroposterior and lateral directions. It is well to note that epiphyseal fractures without displacement often cannot be picked up by roentgenography and are commonly diagnosed as "sprains." Unfortunately these undiagnosed fractures are prone to result in arrest of growth. Forward displacement of the epiphysis is not uncommon and gives a clinical picture similar to the "reversed Colles' fracture" of adult life. An accompanying fracture of the styloid process of the ulna is not uncommon. A soft crepitus may be made out, but it is not necessary for diagnosis and should not be sought for.

Treatment.—When there is no displacement, or after reduction of a slight displacement (which can be done readily without an anesthetic), the hand and forearm are put up in a simple retentive splint for from eighteen to twenty days. Complete displacements should be reduced under an anesthetic by hyperextension, traction and flexion manipulation. There is little tendency for the deformity to recur after complete reduction. The union is more rapid than in Colles' fractures in adults. In complicated cases, an open operation may be necessary. Poland collected four cases in which it was necessary to resect the diaphyseal end of the radius to effect the reduction of the fragments. He mentioned the necessity for resection of the whole or part of the injured radial epiphysis in some cases in which the epiphysis was severely comminuted or when ankylosis appeared certain. He also stated that conjugal chondrectomy, that is, excision of the conjugal cartilage of the ulna, may be performed to produce its arrest of growth in deformity arising from cessation of growth of the radius after epiphyseal injury. This is especially desirable when there is still a considerable period of time before the bone reaches its limit of increase in length.

J. Walton stated that if there is subsequent cessation of growth of the radius after epiphyseal injury, it may be necessary to remove a section of the shaft of the ulna to overcome the resulting deformity of the wrist.

I. Zadek believed that in fractures of the lower radial epiphysis, as against Colles' fractures, there are two smooth surfaces in contact and an absence of interlocking spicules of bone to help maintain the

reduction, and that with the usual upward and backward displacement of the epiphysis of the radius, the epiphysis may be forced into place readily, but there is a strong tendency for the displacement to recur immediately. He recommended a general anesthetic for reduction with maintenance by means of a circular plaster of paris cast with the wrist in 100 degrees palmar flexion for two and one-half to three weeks.

Complications.—Besides the separation of the lower fragment, there may be another fracture line through the epiphysis, or the epiphysis may be severely comminuted although the structure is more resistant than the corresponding portion of the radius in adult life. Laceration of the muscle fibers of the pronator quadratus is mentioned, but only a few fibers are attached to the epiphysis and this complication is unimportant. If the fracture is limited to the epiphysis the wrist joint will always escape injury. However, traumatic arthritis in the wrist may be produced by the exciting cause. The periosteum of the lower diaphysis is usually detached or lacerated and a bit of it may become wedged between the fragments. Accompanying the radial lesion, there may be a fracture of the ulna styloid, but this is not as common as in Colles' fractures. A fracture of the adjacent shaft of the radius frequently occurs. Cases of pressure on the radial and median nerve have been reported. The most important, and not the least frequent, complication arising after an epiphyseal fracture is a disturbance in growth activity. The severity of the resulting deformity is dependent on the degree of injury to the epiphyseal cartilage and its blood supply. Minor injuries to these structures cause retardation of longitudinal growth and more severe injuries produce a premature ossification of the epiphysis to the diaphysis, the resulting degree of wrist deformity being greater the younger the patient is at the time of the accident.

Prognosis.—No cases of non-union have been reported, and, in the uncomplicated cases, union takes place in the second or third week. The resulting wrist function is good. Deformity is usually due to nonreduction or union in a faulty position, and this deformity is usually completely effaced in following years. Arrest of growth causes marked deformity because of the increase in length of the adjacent ulna. DePaoli did not find any evidence of arrested growth after two years in any of his seventeen cases. J. Poland collected eighteen cases of arrested growth. M. K. Smith had twelve cases five of which showed retardation of growth, and of these three had premature ossification. He stated that the prognosis should be guarded because it depends on four factors: (1) the roentgen appearance, (2) the extent of the injury, (3) the reduction and (4) the age of the patient.

E. W. Andrews reported on the medicolegal aspect of premature ossification. He looked up the literature in defense of a fellow practitioner who was being sued for malpractice because of a fracture which

he had apparently adequately reduced when the patient was a child. The patient had developed a marked deformity in later life due to premature ossification of the radial epiphysis.

The literature contains very few references to the treatment for premature ossification of the lower radial epiphysis. Conjugal chondrectomy and osteotomy of the ulna are mentioned as possibilities, but the indications for, and the results of these operations were not mentioned. For this reason it seems worth while to report two cases, in one of which an operation was performed, and in the other no operation, with a follow-up of each.

REPORT OF CASES

CASE 1.—W. F., a boy, aged 12 years, came to the outpatient department of the Fifth Avenue Hospital on Sept. 19, 1929, complaining of weakness and deformity of the left wrist of six years' duration. Seven years previously, when he was 5 years old, he fell from a height of 10 feet (3 meters) into a basement, striking his head and left arm. He was taken to a city hospital. The report from that institution follows:

W. F., a white 5 year old boy, was admitted to the hospital on July 5, 1923, and was discharged on July 7. The diagnosis was a fractured left radius.

History.—The patient was brought to the hospital in a taxicab, and his father stated that he fell about 10 feet, striking on both hands. He got up and ran home, which was about a block away from the accident. He said that his left hand hurt him and he could not use it.

Examination.—There was an abrasion about 2 inches (4.6 cm.) in diameter on his forehead. His upper lip was markedly swollen and there was ecchymosis about both eyes. Dry blood was noted in both nostrils. The pupils were equal but slightly dilated. The left wrist showed the usual appearance of a Colles' fracture. The chest and abdomen were normal.

Diagnosis.—A provisional diagnosis of fractured skull, concussion of the brain and left Colles' fracture was made, and roentgenograms taken of the left forearm showed an oblique fracture through the lower left radial epiphysis *with no displacement.* Roentgenograms of the skull showed no evidence of fracture.

Treatment.—An anterior molded splint was applied, and the patient was put to bed. His pulse was taken every hour, showing a rate of between 100 and 110. His temperature remained normal and he was conscious all the time and took nourishment well. He remained in the hospital for two days and was then taken home. After two weeks the splint was removed and his condition was considered satisfactory.

Subsequent History.—For the first year or two after the accident, there was no apparent difficulty with the left wrist. Then the mother noted a very slight deformity which slowly became more noticeable up to one year ago, when it was quite obvious that something was wrong. During the past year the deformity rapidly became more pronounced, and the patient began to complain of weakness in his left hand. In August, 1929, he went to another hospital where roentgenograms were taken and the old fracture was recognized. Considerable deformity of the left wrist was present at that time. He was advised to return for observation

over a period of months to determine the extent of the epiphyseal injury. This he did not do, and the following month he was admitted to the Fifth Avenue Hospital.

Physical Examination.—The general appearance was that of a husky boy of 12 years. The routine examination gave negative results except for the local condition. The results of laboratory examinations were negative. Local condition: The left forearm as well as the left hand was smaller than the right. The left forearm was 1¾ inches (3.3 cm.) shorter than the right as measured from the olecranon to the tip of the middle finger. The musculature of the left hand and forearm was less well developed than that of the right, and the left hand showed a marked radial deviation. The lower end of the ulna protruded downward and outward. The left grip was weaker than the right. Ulnar deviation was limited while radial deviation was increased. Pronation and supination were not limited,

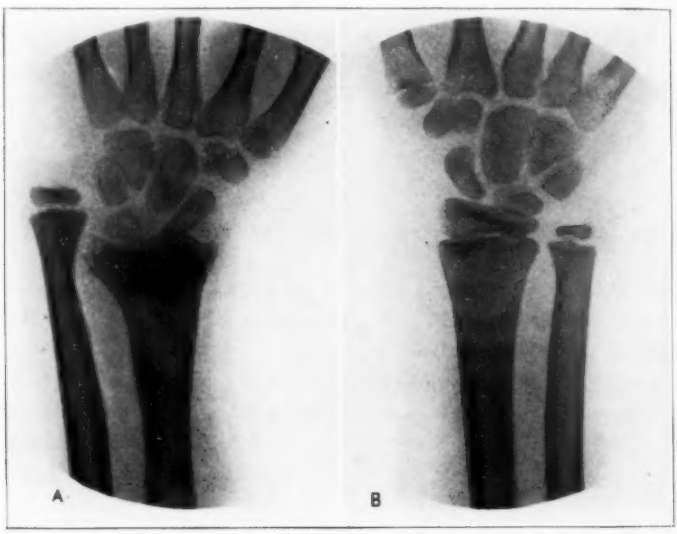

Fig. 1.—*A*, roentgen appearance of the injured wrist in case 1, six years after the accident. It shows the premature ossification of the lower radial epiphysis and the increase in ulnar length; also the radial deviation deformity. *B*, the normal wrist.

and flexion and extension were only slightly limited by weakness. The radioulnar attachments were loose and allowed free up and down movement of either bone. The lower end of the radius presented a roughened, irregularly prominent, bony thickening.

A provisional diagnosis of old injury to the lower radial epiphysis with retardation of growth was made.

Roentgen examination (fig. 1 *A*) showed an old fracture through the lower end of the radius which was apparently markedly impacted. The lower end of the radius was spread outward and cupped. The epiphysis had been destroyed or at least rendered inactive as the ulna had lengthened, so that the styloid process was approximately three fourths of an inch (1.90 cm.) lower than the articular surface of the lower end of the radius, thus causing deviation of the carpus toward

the radial side of the forearm. Roentgen measurements showed the left ulna to be 18.5 cm. in length and the right 20.5 cm.; the left radius, 14.75 cm., and the right 19.75 cm.

The patient was admitted to the hospital on Sept. 23, 1929, and discharged on October 26. On September 27, under general anesthesia, a 2 inch (5.08 cm.)

Fig. 2.—*A*, the periosteal thickening about the amputated end of the ulna. *B*, roentgenogram of the normal forearm and wrist showing the greater length as compared with side on which the operation was performed.

longitudinal incision was made medial to the distal end of the left ulna. At a point judged to be at the level of the lower radial articulation the ulna was cut through with a Gigli saw and the lower fragment excised. A few thinned-out fibers of the pronator quadratus were stripped from the lateral surface. No nerves or large blood vessels were cut. The wound was closed without drainage, and

anterior and posterior molded plaster of paris splints were applied with the hand in the cock up position and ulnar deviation. The patient was examined roentgenologically on leaving the operating room, and the following report was made: "Films of the left wrist show that the lower end of the ulna has been removed so that its lower margin is about on a level with the lowest point of the articular surface of the radius."

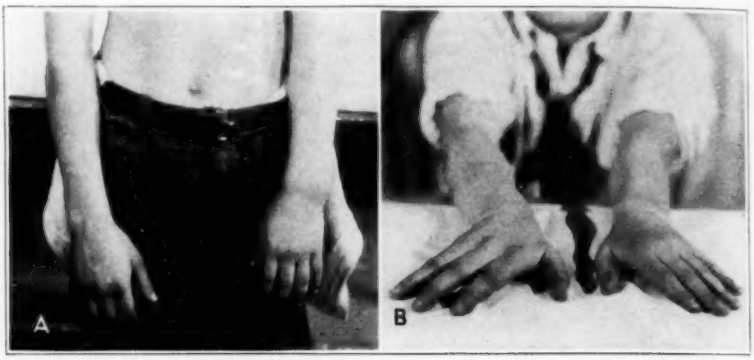

Fig. 3.—*A*, postoperative appearance, showing the shortening of the left forearm. *B*, photograph showing the ulnar deviation of the left wrist practically equal to that of the right wrist.

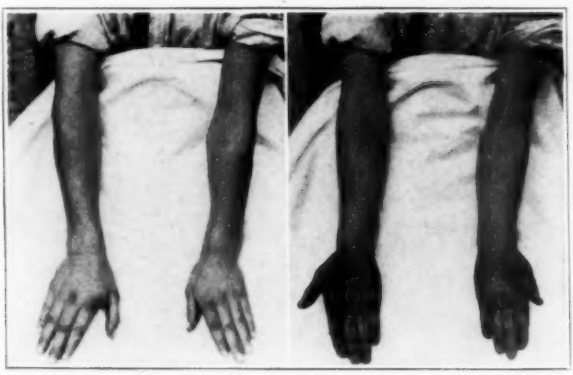

Fig. 4.—Appearance of the arm fifteen months after operation.

Postoperative Course.—The wound healed by primary union, and, except for a small blister on the anterior surface of the wrist due either to iodine or to the closely applied splints and a slight, temporary, unexplained rise in temperature on the seventeenth postoperative day, the patient made an uneventful recovery. Chest films taken during the temperature elevation were negative for lung involvement. The splints were discarded on the twelfth postoperative day, and exercises, baking and massage were started.

Pathologic examination of the excised epiphysis was not done because it was apparently normal. The patient was discharged from the hospital on the twenty-ninth postoperative day.

Follow-Up Examination.—One month after the operation, the patient's wrist motion was good and there was a decided increase in the degree of ulnar deviation

Fig. 5.—Roentgen appearance of both arms fifteen months after operation.

and wrist strength. A conspicuous, firm, thickening about the lower end of the ulna was noted and a roentgenogram (fig. 2 *A*) taken at that time showed a smoothened lower ulnar surface and a periosteal thickening. Pronation and supination were considerably limited because of the periosteal reaction at the lower end of the ulna. The general appearance of the left arm as compared with the right is shown by the photographs (fig. 3) taken at this time.

Ten weeks after operation the following measurements were taken:

	Left, Cm.	Right, Cm.
Circumference of wrist	15.0	14.0
Length from olecranon to tip of middle finger	33.0	37.5
Circumference at level of metacarpophalangeal joint	15.5	17.5
Circumference of forearm	17.5	18.5
Circumference at elbow	19.5	21.0
Length of radius (roentgenogram)	14.7	19.7
Length of ulna before operation (roentgenogram)	18.5	20.5
Length of ulna after operation (roentgenogram)	16.7	20.5

Fig. 6.—The deformity in case 2, resulting from premature ossification of the lower radial epiphysis.

Five months after the operation the left wrist showed good function and strength, ulnar deviation being only slightly limited. Fifteen months after the operation there was practically no limitation of strength or mobility in the left wrist; the patient was playing basket ball and had even engaged in several fist fights with considerable success.

CASE 2.—J. R., a man, 38 years old, an Italian, came into the hospital for resection of a growth in the large bowel. A deformity of the left forearm was noted and the following typical history was obtained:

At the age of 5 years he was sliding down a banister when he fell, landing three flights below. He was unconscious when picked up and was suffering from a lacerated scalp and fractured left forearm and knee. He was treated in his home where he remained in bed for one month. During that time four attempts

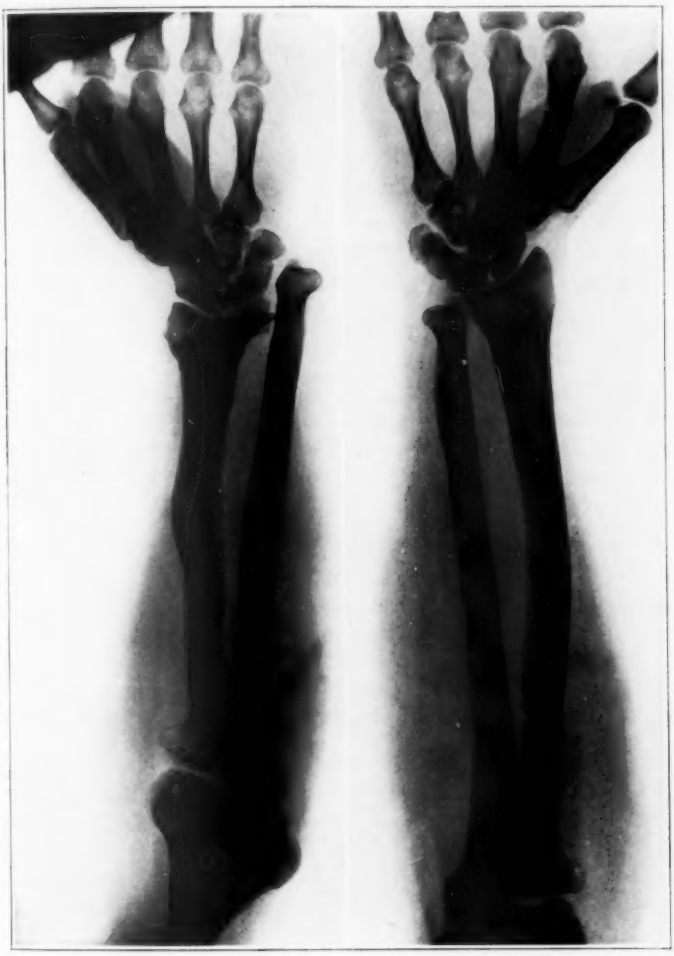

Fig. 7.—Roentgen appearance of both forearms in case 2.

were made to reduce the fractured forearm. During the next nine years he had no further trouble. At the age of 14, a lump on the left wrist was first noted, together with some weakness as compared with the right. Later he noted that the left arm was shorter than the right. The weakness persisted, but did not handicap him in his typewriting. Figure 6 shows the marked shortening of the left forearm as compared with the right.

CONCLUSIONS

1. Even after adequate reduction of an epiphyseal fracture a premature ossification with a resultant wrist deformity may ensue.

2. A follow-up of these fractures should extend over a period of at least two years.

3. Conjugal chondrectomy should be done as soon as a definite diagnosis of premature ossification can be made; this requires careful observation and frequent roentgenograms of both forearms.

4. The amount of longitudinal growth to be expected from the upper epiphysis of the radius is small, so the ulna should be excised at the level of the articulating surface of the radius.

5. Conjugal chondrectomy is a simple procedure and gives a well functioning wrist. If done early enough it would probably prevent muscle weakness and atrophy.

BIBLIOGRAPHY

Andrews, E. W.: Ann. Surg., May, 1902, p. 663.

Bonta, Emile: Du décollement épiphysaire traumatique de l'extrémité inférieure du radius, Thèse de Paris, 1906.

Cohn, Isidore: X-Ray Appearance of the Developing Joints and Epiphyses, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1928, vol. 2, chap. 3.

Cotton, Frederic J.: Separation of the Radial Epiphysis, ibid., vol. 2, chap. 4, p. 83.

Goodhue, E. S.: Operation for the Correction of Deformity of the Wrist Caused by Shortening of the Radius After Fracture, New York M. J., Jan. 6, 1894, p. 9.

Haas, S. L.: Experimental Transplantation of the Epiphysis with Observations on the Longitudinal Growth of Bone, J. A. M. A. **65**:1965 (Dec. 4) 1915.

Metenier, E.: Contribution à l'étude du décollement épiphysaire à l'extrémité inférieure du radius, Thèse de Paris, 1906-1907.

Montgomery, Albert H.: Separation of Upper Epiphysis of Radius, Arch. Surg. **10**:961 (May) 1925.

Poland, J.: Traumatic Separation of the Epiphyses, London, Smith, Elder & Company, 1898, p. 478.

Scudder, C. H.: Treatment of Fractures, Philadelphia, W. B. Saunders Company, 1926, ed. 10, pp. 380, 438 and 1062.

Smith, M. K.: The Prognosis in Epiphyseal Line Fractures, Ann. Surg. **76**:273 (Feb.) 1924.

Premature Ossification After Separation of the Lower Radial Epiphysis, Ann. Surg. **75**:501 (April) 1922.

Speed, Kellog: Fractures and Dislocations, Philadelphia, Lea & Febiger, 1916, p. 88.

Stevenson, Paul H.: Age Order of Epiphyseal Union in Man, Am. J. Phys. Anthropol., January-March, 1924, vol. 7, no. 1.

Stimson, L. A.: A Textbook of Fractures and Dislocations, ed. 8, Philadelphia, Lea & Febiger, 1917, p. 29.

Walton, A. J.: Fractures and Separated Epiphyses, London, E. Arnold Company, 1910, vol. 7, p. 288.

Zadek, Isadore: Treatment of Epiphyseal Separation of the Lower End of the Radius, Arch. Surg. **10**:969 (May) 1925.

INCIDENCE OF NODULES IN THE THYROID

A COMPARATIVE STUDY OF SYMPTOMLESS THYROID GLANDS REMOVED AT AUTOPSY AND HYPERFUNCTIONING GOITERS OPERATIVELY REMOVED *

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MINNEAPOLIS

The presence of nodules within an otherwise normal thyroid gland is well recognized. Whether or not these nodules have any definite significance has long been a debated question. It has been thought that they represent developmental processes that occur in the natural course of development and indicate no significant feature. They have also been considered as involutional bodies, representative of the stages in hyperthyroid diseases, and they have been looked on as true tumors arising from germinal centers and having the significance of benign neoplasms. Whichever may be the case, their definite significance has never been proved.

If one is to establish the normal for a given district by assuming that the majority represents the normal, then one must accept the presence of nodules in the thyroid gland as a normal characteristic in Minnesota. It is, however, more probable that these nodules represent an attempt to establish a physiologically normal gland, and to that extent they may be considered physiologically normal.

The presence of nodules in goitrous thyroid glands has likewise been a controversial point. Any proof to indicate their etiologic significance has not been definitely established.

A comparative study of the incidence of nodules in a postmortem series without symptoms referable to the thyroid gland and in hyperfunctioning goiters removed at operation would be of interest and may be able to throw some light on the reason for their existence. With that point in view, this study has been undertaken. The operative specimens constitute the group of cases classified as exophthalmic goiter and hyperfunctioning adenomatous goiter. The postmortem series is composed of supposedly normal thyroid glands removed from unselected patients dying of diseases other than those of the thyroid gland.

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REVIEW OF THE LITERATURE

Goiter is found in all parts of the world, but its incidence may vary greatly in different localities. In Europe the goiter districts are known to comprise southern France, southern Germany, Switzerland, southern Austria and northern Italy. Within these goitrous districts the incidence is likewise exceedingly variable. Steiner,[1] in reviewing the goiter situation in Switzerland, demonstrated that the incidence of goiter in different cantons may vary from 5.7 per cent to 80.4 per cent. In Spain, Maranon [2] pointed out that all the mountainous districts exhibit goiter, often representing an incidence as high as 25 per cent. In Asia practically all of the Himalaya districts are in a goitrous belt, the incidence being as high as 20 per cent in some localities. Hirsch [3] pointed out the presence of goiter in the region of the Andes Mountains in South America and in Central America.

In the United States goiter is found endemic in the northern states, most frequently in the Pacific Northwest and in the regions of the Great Lakes. This geographic distribution is illustrated by Carter [4] in his material collected from the draft board statistics. From these figures it is found that 80.4 per cent of the drafted men presented thyroid enlargement. These figures are confronted with numerous possibilities for error and would be worthless if taken individualiy to represent the incidence of goiter in any particular locality. But collectively, they indicate the general trend of the distribution of thyroid enlargement. Olesen and Clark [5] studied the incidence in Minnesota and found that of 4,061 students examined between the ages of 5 and 23 years, 40 per cent of the boys and 71 per cent of the girls had enlargement of the thyroid gland.

The parallelism between the diffuse goiter and nodular goiter is very evident in some localities, whereas in others it is quite divergent, as Steiner [6] has shown in Switzerland. In one canton where goiter was

1. Steiner, Otto: Der Kropf bei den Stellungspflichtigen der Jähre 1924 und 1925, Schweiz. med. Wchnschr. **58**:401, 1928.

2. Maranon, G.: The Present Status of the Problem of Endemic Goiter in Spain, in International Conference on Goiter, New York, Paul B. Hoeber, Inc., 1927, p. 361.

3. Hirsch, August: Handbook of Geographical and Histological Pathology, Stuttgart, Ferdinand Enke, 1885, vol. 2, p. 121.

4. Carter, Ezra, G.: Simple Goiter: Thesis for the degree of Doctor of Philosophy, Univ. Michigan, 1925.

5. Olesen, R., and Clark, T.: Thyroid Enlargement Among Minnesota School Children, Pub. Health Rep. **39**:2561 (Oct. 10) 1924.

6. Steiner, Otto: On the Diffusion of Endemic Goiter in Switzerland, in International Conference on Goiter, New York, Paul B. Hoeber, Inc., 1927, p. 393.

found in 41 per cent of the inhabitants, he found that 31 per cent were nodular goiters, whereas in another canton where 51.1 per cent of the inhabitants had goiter, only 3.3 per cent contained nodules.

Aschoff [7] pointed out that nodules are found in thyroid glands in northern Germany, a nongoitrous district, just as frequently as they are in southern Germany, but that those in the goitrous districts are much larger. He suggested that the nodule is a sort of tumor rest that exists in every human thyroid gland, but that these tumor rests show intensive growth only under favorable stimulation, whatever that stimulation may be.

ADENOMAS IN THE THYROID GLAND

The adenomas have been generally classified into two main groups, the colloid adenoma and the fetal adenoma. The consensus as to what constitutes a colloid adenoma is well established; namely, that it is a localized area with proliferative or involutional changes of the follicle with large colloid-containing acini, usually encapsulated. The histologic structure may be in all respects similar to that of the normal parenchyma, except that there is no separation into lobules by fibrous tissue stroma, as is seen in the normal thyroid gland.

Fetal adenomas are those in which the structure resembles that seen in the fetal thyroid gland. Wegelin [8] referred to them as parenchymatous nodules, and classified them into three types according to their structure, calling them trabecular, tubular and small follicular adenomas. He, however, considered them all fundamentally the same.

Intermediate nodules are those exhibiting characteristics of each of the other two types within its structure, as described by Bell.[9]

Degenerate nodules constitute all those in which degenerative changes have occurred, as cystic, fibrous, hyaline, calcareous, hemorrhagic, etc. Originally these may have been any one of the other types of nodules that had undergone degenerative changes. Woelz,[10] in making a comparative study of the various types of goiter in Basel and Berne, observed that degenerative changes were found more frequently in the goiters of Basel than in those of Berne. She believed that this could

7. Aschoff, Ludwig: Pathologic Anatomy of Endemic Struma, in International Conference on Goiter, New York, Paul B. Hoeber, Inc., 1927; The Goiter Problem, Especially the Goiter of Puberty, in Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1925.

8. Wegelin, C.: Die Schilddrüse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

9. Bell, E. T.: Textbook of Pathology, Philadelphia, Lea & Febiger, 1930.

10. Woelz, Emilie: Vergleichende Untersuchungen über die Haufigkeit der vershiedenen Kropfformen in Basel und in Berne, Schweiz. med. Wchnschr. **51**:625, 1921.

be explained by the fact that colloid nodules are more prone to develop degenerative changes than the fetal type of nodule. The latter are found more frequently in the goitrous district of Berne, whereas colloid nodules are found more frequently in Basel, which lies toward the periphery of the region endemic for goiter.

There are two prevailing opinions with regard to the formation of adenomas. That formulated by Wölfler [11] and Ribbert [12] postulates that adenomas of the thyroid arise from embryonal cell rests scattered throughout the thyroid tissue. Wölfler has classified these types of adenoma as fetal because of their similarity in structure to that of the thyroid in the fetus. His conclusions were based on operative material of fully developed goiters, deducing from their histologic structure his conclusions that the nodules arose from embryonal cell rests. Hitzig [13] and Michaud,[14] investigating the structure of adenomatous goiters and examining many from young persons, came to the conclusion that the nodules were not embryonal rests, but that they developed from normal thyroid tissue by metaplasia of the epithelial cells within a localized area replacing the normal tissue, thereby forming a complete secondary lobule or nodule. More recently Kramer,[15] Vogel,[16] Hueck,[17] Kline [18] and others have expressed the same opinion.

Aschoff is of the opinion that nodules develop as tumors and not as localized hypertrophy and hyperplasia. Kramer observed that the epithelial proliferation that leads to the formation of adenomas has its origin in the centrally situated follicles of the thyroid lobule. Aschoff called these centrally situated follicles canaliculi, and expressed the belief that they are rests of germ material from which the other follicles

11. Wölfler, Anton: Ueber die Entwicklung und den Bau des Kropfes, Arch. f. klin. Chir. **29**:1, 1883.

12. Ribbert, Hugo: Das Adenom der Schilddrüse, Frankfurt. Ztschr. f. Path. **18**:55, 1916.

13. Hitzig, Theodor: Beiträge zur Histologie und Histogenese der Struma, Arch. f. klin. Chir. **47**:464, 1894.

14. Michaud, Louis: Die Histogenese der Struma nodosa, Virchows Arch. f. path. Anat. **186**:422, 1906.

15. Kramer, L.: Ueber die Rückbildungsvorgänge in den Schilddrüsen Adenomen, Inaug. Diss., Frieberg, 1910, quoted by Wegelin, C.: Die Schilddrüse, in Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

16. Vogel, Herbert: Beiträge zur pathologischen Histologie der Schilddrüse, Virchows Arch. f. path. Anat. **217**:204, 1914.

17. Hueck, Herman: Ein Beitrag zur Beurteilung der Knoten in der Schilddrüse, Deutsche Ztschr. f. Chir. **174**:185, 1922; Zur Frage des Parellelismus zwischen klinischen und histologischen Bild der Struma, Arch. f. klin. Chir. **130**:178, 1924.

18. Kline, B. S.: The Origin of Adenomatous Goiter, Am. J. Path. **1**:235, 1925.

of the thyroid have developed. Bürkle de la Camp [19] was of the same opinion. In referring to the development of colloid nodules, Rienhoff [20] spoke of involutional bodies, and he believes that these areas represent a stage in the disease of hyperthyroidism. Hertzler [21] referred to them as bosselated areas on a similar basis.

Graham [22] expressed the belief that the development of nodules can be explained by a single process rather than by multiple processes or mechanisms of fundamentally different character. He believes that there is a difference in degree of reversion, growth, differentiation and encapsulation which produces the various gross and microscopic pictures that may be observed in nodular goiter. He considered nodular goiter related to the hyperplastic phases of thyroid overgrowth, and that the process of nodular formation may have its inception at any stage in the life of the individual. Wangensteen [23] observed that the blood supply in the region of an adenoma or in the region of degenerating areas is usually poor. This may also be a factor in the development of adenomas.

INCIDENCE OF NODULES

Nodules occur infrequently in the thyroid glands of young persons, but Wegelin [8] found 1.9 per cent in those of children under 10 years of age. The thyroid glands of more than half of the persons in Berne over 20 years of age have nodules, and in persons over 60 years of age it is uncommon to find glands without nodules. Wegelin found 73.3 per cent in men and 88.4 per cent in women over 25 years of age. Jaffé [24] found in the region of Chicago that nodules occurred in 30 per cent of men and 44.7 per cent of women over 20 years of age. He

19. Bürkle de la Camp: Einteilung der strümosen Erkankungen des Schilddrüse von pathologisch anatomischen Gesichtspunken aus unter Berücksichtigung ihrer klinischen, Erscheinungen, Arch. f. klin. Chir. **130**:207, 1927.

20. Reinhoff, W. F., Jr.: Thyroid Gland, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1928, vol. 6, chap. 1; Gross and Microscopic Structure in Thyroid Gland in Man, Arch. Surg. **19**:986 (Dec.) 1929; Histologic Changes Brought About in Case of Exophthalmic Goiter by Administration of Iodine, Bull. Johns Hopkins Hosp. **37**:285, 1925. Reinhoff, W. F., and Lewis, D.: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79 (Jan.) 1928.

21. Hertzler, A. E.: Diseases of the Thyroid Gland, St. Louis, C. V. Mosby Company, 1929.

22. Graham, A.: Nodular Goiters; Their Relation to Neoplasia, Am. J. Surg. **7**:163, 1929.

23. Wangensteen, Owen H.: The Blood Supply of the Thyroid Gland with Special Reference to the Vascular System of the Cretin Goiter, Surg., Gynec. & Obst. **48**:613, 1929.

24. Jaffé, R. H.: The Variation in Weight of the Thyroid Gland and the Frequency of Its Abnormal Enlargement in the Region of Chicago, Arch. Path. **10**:887 (Dec.) 1930.

referred to the fact that there is a constant increase in the frequency of nodules with advancing age. The work of Klöppel, Davidsohn,[25] Clerc [26] and Hueck [17] would also indicate that the incidence of nodules increases with advancing age. Hellwig [27] made a comparison between goiters from North America and goiters from Switzerland, and he came to the conclusion that there is a definite difference between them, particularly in the percentage of the various types of goiter. Basing his work on operatively removed specimens, he found that 47 per cent of the goiters from Kansas contained nodules, whereas in his cases studied in Freiburg, the incidence of nodules was 77 per cent, and in Rostock it was 32 per cent.

Woelz,[10] in calculating the relative frequency of the various types of goiter occurring in Switzerland, as based on the histologic examination of operatively removed specimens from Basel and Berne, showed that 92 per cent of the cases were nodular.

METHOD OF COLLECTING AND PREPARING MATERIAL

The material used was collected at the University of Minnesota from the Minneapolis General, the Ancker and the University hospitals between January, 1929, and January, 1931. It represents 390 glands removed post mortem and 165 glands removed at operation. The cases were collected from corresponding age groups and from corresponding localities, and represent a fair distribution for the state of Minnesota.

The postmortem series includes the glands of persons dying of numerous causes. No attempt was made to select the patients, except to exclude those who presented a definite history of hyperfunctioning thyroid disease or in whom there was a very evident goiter on casual inspection post mortem. Large glands that were not observed before removal of the gland were not excluded from the series. All of the operatively removed glands were taken from patients on whom thryoidectomy was performed for hyperfunctioning thyroid disease. This included exophthalmic goiter and adenomatous goiter with hyperthyroidism. The ages of the persons from whom the thyroid glands were obtained ranged between 11 and 75 years. This distribution is indicated in table 1. A definite prevalence of males can be observed in the postmortem series, whereas a definite prevalence of females can be observed in the postoperative series.

All glands were cut into sections 3 mm. thick and examined grossly. The number of nodules were counted in each gland and their size measured in millimeters. Where more than one nodule was found in each gland, the average size was tabulated. The type of nodule was determined by gross and microscopic

25. Davidsohn, Carl: Der Bau der Kröpfe und seine Bedeutung für Function und Krankheit, Berl. klin. Wchnschr. **48**:2070, 1911; Ueber den Schlesischen Kropf, Virchows Arch. f. path. Anat. **205**:170, 1911.

26. Clerc, Edward: Die Schilddrüse in hohen Alter, von 50 Lebensjahr an aus der norddeutschen Ebene und Küstengegend sowie aus Berne, Frankfurt. Ztschr. f. Path. **10**:1, 1922.

27. Hellwig, C. Alex.: Morphological Changes in Exophthalmic Goiter Following the Use of Lugol's Solution, Surg., Gynec. & Obst. **27**:173, 1928; Form und Funktion des nordamerikanischen Kropfes, Arch. f. klin. Chir. **154**:1, 1929.

examinations. Because of the great discrepancy in the number of cases in the male between the two series, only the female glands were used in these calculations. It is assumed that if satisfactory comparisons could be made of the male glands, similar results would be observed.

THE WEIGHT OF THE THYROID GLANDS

The average weight of the thyroid glands in the postmortem series was less than that in the postoperative series. The average weight of glands with nodules, post mortem, was 42.02 Gm., and postoperatively was 99.55 Gm. The average weight without nodules, post mortem, was 25.99 Gm., and postoperatively was 61.79 Gm.

It is to be remembered, however, that in the postoperative series, from one fourth to one half of a normal-sized lobe was allowed to

TABLE 1.—*Distribution According to Age in the Postmortem and Postoperative Series*

Ages	Postmortem Series Number of Cases		Postoperative Series Number of Cases	
	Female	Male	Female	Male
11–15	7	1	1	0
16–20	13	7	3	3
21–25	10	8	18	2
26–30	10	12	13	2
31–35	10	11	18	0
36–40	19	15	21	5
41–45	16	15	20	3
46–50	14	21	18	6
51–55	12	30	12	0
56–60	14	25	6	3
61–65	13	31	2	1
66–70	10	39	6	0
71–75	3	24	2	0
Total	151	239	140	25

remain, and therefore these weights give only an indication of the definite increase in size of the thyroid gland in goiters and do not represent the actual weight of the goitrous thyroid glands.

A wide range of variability was observed in both series of cases, but the postmortem series appeared to lie within a definite limit of from 10 to 65 Gm., whereas the postoperative series ranged from 10 to 300 Gm. or more. The glands containing nodules had a wider range of variability in weight than those without nodules.

NODULES

Incidence of Nodules.—The incidence of nodules in the postoperative series was 57.14 per cent, and in the postmortem, 56.95 per cent. As the individual becomes older, the incidence of nodules becomes greater. This increase in the incidence with advancing age was observed in both series, so that in persons between 70 and 75 years of age 100 per cent

of the glands are found to contain nodules. A comparison of the incidence of nodules as found by Klose [28] and Hellwig with this series will be of interest.

Number of Nodules per Gland.—The number of nodules per gland was variable in the two series, the significance of which cannot be definitely established. Their incidence is observed in table 3, as well as a comparison of these results with Hellwig's incidence for Kansas.

The discrepancy of the figures in the two series indicating fewer multiple nodules in the operatively removed glands than in the glands removed post mortem may be due to the fact that nodules were occasionally allowed to remain in the portion of the gland that was not removed, as would occur in simple enucleation of one nodule or in the

TABLE 2.—*Incidence of Nodules in the Material of Three Investigations*

	Klose		Hellwig		Present Series	
	Frankfort, per Cent	Freiburg, per Cent	Rostock, per Cent	Kansas, per Cent	Postmortem, per Cent	Postoperative, per Cent
Diffuse.....	56	23	68	53	43.05	42.86
Nodular.....	44	77	32	47	56.95	57.14

TABLE 3.—*Incidence of Nodules in Glands Removed Post Mortem and at Operation and Comparison of These Results with Hellwig's Series*

	Present Series				
	Postmortem, per Cent		Postoperative, per Cent		Hellwig Postoperative
One nodule per gland.....	26.7		36.7		13 (27.6%)
More than one but less than twelve.....	37.2	73.2	20.26	63.29	
More than twelve nodules.....	36.0		43.03		
Multiple nodules	....		....		34 (72.4%)

resection of only one lobe. This would seem to indicate, however, that the multiplicity of nodules was not increased as a result of the presence of hyperthyroidism, as has been suggested by Rienhoff.

Size of Nodules.—The size of the nodules in the postoperative series was distinctly larger than in the postmortem series, but they did not appear to have any definite size for any age period, as has been previously demonstrated to occur during the life cycle of the normal thyroid gland.[29] Their variability in size was just as marked in the younger ages as in the older ages. In the postmortem series the average size of the nodules was

28. Klose, Heinrich: Die pathologisch anatomischen Grundlagen der Basedowschen Krankheit, Bruns' Beiträge z. klin. Chir. **102**:1, 1916. Klose, H., and Hellwig, A.: Ueber Bau und Funktion der kindlichen Schilddrüsen-Hyperplasia, Arch. f. klin. Chir. **124**:347, 1923.

29. Rice, C. O.: The Life Cycle of the Thyroid Gland in Minnesota, West. J. Surg. **39**:925 (Dec.) 1931.

seen to increase during puberty, to decrease during early adult life and to increase again after 35 years of age, reaching the maximum at 65 years, after which the nodules decrease slightly to the end of the life span. A similar curve could not be detected in those in the postoperative series. This would be expected, however, for here the normal cycle of the gland has been interrupted by disease.

Types of Nodules.—The percentage of the various types of nodules in the adenomatous glands is stated in table 4, which does not imply that each gland contained only one type of nodule, for very often all types of nodules were found in each gland. If one is to consider the glands that contained only one type of nodule within its structure, the proportions cited in table 5 were observed.

TABLE 4.—*Percentage of Types of Nodules in Adenomatous Glands*

	Postmortem Series, per Cent	Postoperative Series, per Cent
Colloid	82.5	66.25
Fetal	25.5	38.75
Mixed	6.9	25.00
Degenerate	15.1	37.50

TABLE 5.—*Percentage of Glands with Only One Type of Nodule*

	Present Series				Hellwig		Woelz				
	Postmortem		Postoperative		Kansas		Berne		Basel		Wydler Berne,
	No.	%	No.	%	No.	%	No.	%	No.	%	%
Colloid	54	62.79	22	27.5	29	62	14	23.64	261	55.0	9
Fetal	8	9.3	10	12.5	12	25	147	46.9	47	9.9	64
Mixed	2	2.32	7	8.75	..	..	....	....	....	....	..
Degenerate	3	3.48	6	7.5	..	..	....	....	....	....	..
Multiple types	19	22.09	35	43.75	6	13	92	29.4	166	35.0	27

The significance of this difference in the various types of nodules in the postoperative and postmortem series can only be postulated. It may be that the same factors that produce hypertrophy and hyperplasia also produce an effect on the nodule which changes its structure from that of a colloid nodule to one of the other types, for it is observed that the colloid nodule is decreased in number, whereas the fetal, mixed and degenerate nodules are increased in number in the operative specimens. This would correspond to the idea of Graham, who deduced that other types of nodules are an involutional or degenerative stage of a colloid nodule. He expressed the belief that the development of nodules is dependent on a single process, and that the difference in degree of reversion, growth, differentiation, encapsulation, etc., offers a satisfactory explanation of the gross and microscopic variations observed in nodular goiters. This conception makes it unnecessary to explain the development of nodules on a fetal rest theory.

INCIDENCE OF VARIOUS TYPES OF GOITERS

In dividing the postoperative series into three groups, those showing diffuse hypertrophy without nodules, diffuse hypertrophy with nodules and adenomatous goiters, with hyperthyroidism, the percentages given in table 6 were observed.

It is seen that 65 per cent were exophthalmic goiters. Thirty-three and eighty-four hundredths per cent of these exophthalmic goiters contained nodules within their structure.

Lymphocytic foci were found in 9.8 per cent of the glands examined post mortem and in 67.85 per cent of the glands examined postoperatively. Seventy-nine and twelve one-hundredths per cent of the exophthalmic goiters contained lymphocytic foci, and 46.93 per cent of adenomatous goiters with hyperthyroidism contained lymphocytic foci.

Wilson [30] has shown that there is a small but definite difference between adenomatous goiters that presented symptoms of hyperthyroidism and those that were nontoxic. In examining approximately 250 cases of each group, he found that in those which had presented symptoms of

TABLE 6.—*Incidence of Various Types of Toxic Goiters*

	Per Cent	
Diffuse hypertrophy (exophthalmic goiter) without nodules	42.85	64.99
Diffuse hypertrophy (exophthalmic goiter) with nodules	22.14	
Adenomatous goiter with hyperthyroidism	35.00	

hyperthyroidism, 90 per cent showed microscopic evidence of hypertrophy and hyperplasia, and in the nontoxic group, 95 per cent showed no evidence of hypertrophy and hyperplasia. He compared the most marked evidences of hypertrophy and hyperplasia in toxic adenomas with those of exophthalmic goiter of the mildest degree, and concluded that in the toxic group the hyperthyroid symptoms could be due to the proliferative changes and increased secretion of toxic material, whereas in the nontoxic group there is not a sufficient amount of this substance secreted to cause the hyperthyroid symptoms.

CONCLUSION

Nodules occur as frequently in the postmortem thyroid gland that is assumed to be physiologically normal as in hyperfunctioning goiter operatively removed. The greater prevalence of colloid nodules in the postmortem thyroid gland may be due to the fact that differences in the degree of reversion, growth, differentiation and encapsulation have not been forced on the normal gland as strongly as they have in the

30. Wilson, L. B.: The Pathology of Nodular Goiters in Patients With and in Those Without Symptoms of Hyperthyroidism, Am. J. M. Sc. **165**:738, 1923.

toxic goiter. Multiple nodules are not found more frequently in hyperfunctioning goiters than they are in physiologically normal thyroid glands. Nodules are found in 56.95 per cent of the physiologically normal thyroid glands and in 57.14 per cent of the toxic goiters. Forty-two and eighty-five hundredths per cent of the toxic goiters have no nodules and are manifested as exophthalmic goiter. Thirty-five per cent of the thyroid glands that become hyperfunctioning can be classified as adenomatous goiter with hyperthyroidism. The remaining 22 per cent of glands contain nodules, but manifest their hyperthyroidism as exophthalmic goiter. Diffuse hyperplastic goiter (exophthalmic goiter) occurs proportionately as frequently in glands with nodules as in glands without nodules. Lymphocytic foci are found more often in hyperfunctioning goiters than in normal thyroid glands. From these observations it appears that the presence of nodules in the thyroid gland is physiologically normal, and that the incidence is not appreciably altered by the development of hyperthyroidism.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomalies.—Jacobs [1] stated that in horseshoe kidney either the upper or lower poles of both kidneys fuse, the latter condition being more common. The parenchyma of the fused part which lies anterior to the great vessels varies in amount. The ureters, usually two, arise from separate pelves and pass anterior to the isthmus, but because of their unusual position and curvature the kidneys are predisposed to obstruction, infection and stone.

Jacobs reported two cases of horseshoe kidney. In the first case, albuminuria led to a roentgenographic examination and the discovery of calculus. Bilateral pyelographic examination disclosed the lateral position of the ureteropelvic juncture. The isthmus was divided at operation, but a urinary fistula persisted due to cutting across a calyx in the resected portion of the isthmus. In the second case, there was backache and hematuria, with hydronephrosis on the left side and the calices directed mesially. The right kidney was normal. Operation was not performed.

Operation in cases of horseshoe kidney is materially assisted by a previous knowledge of the existence of the condition. Bilateral pyelograms are the best means of making a diagnosis. Abnormalities are due to failure of rotation of the renal pelvis. The axis of the calices is median or anterior, and the ureter leaves laterally or anteriorly.

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1. Jacobs, Arthur: Horseshoe Kidney: A Report of Two Cases, Brit. M. J. **2**:8 (July 5) 1930.

[ED. NOTE.—In one of these cases a urinary fistula persisted after resection. It is only rarely that a portion of the pelvis or one of the calices extends down into the isthmus. If this area is sutured over, fistula seldom results. There have been few cases reported of fistula occurring after resection. In one case a large pelvic stone extended down into the isthmus. Accurate closure was carried out; there was no urinary leakage.

As the author stated, the correct diagnosis of renal anomalies, especially of horseshoe kidney, materially affects surgical prognosis. The abnormal structural relations, the unusual attachments and the unrotated position of the renal pelvis require a surgical approach different from that employed in dealing with kidneys normally situated. The numerous and anomalous blood vessels, and the fixity and situation of the renal mass necessitates accurate anatomic recognition of the condition for the carrying out of any successful surgical procedure.]

Collins [2] summarized the data in 581 cases of congenital unilateral renal agenesia, which were divided about equally between men and women. The kidney was absent on the left side in 318 cases, on the right side in 238, and the side was not stated in 25. The average weight of the remaining kidney in 87 cases was about 280 Gm. (normal, 150 Gm.). The remaining kidney was normal in 281 cases, diseased in 179 and the condition was not stated in 121. In 110 cases death was due to disease of the genito-urinary tract. The condition was diagnosed at necropsy in 439 cases, by clinical and surgical methods in 124 cases and in 18 it was not stated. There were anomalies of the internal genitalia in 338 cases. One ureter was absent in 297 cases, and other ureteral anomalies were observed in 284 cases.

In 65 per cent of cases noted in the literature, congenital absence of one kidney was observed in subjects whose average age was 40 years; 68 per cent of these had died of diseases totally unrelated to the genito-urinary system. In the presence of disease of the genito-urinary system, extensive surgical procedures on the urinary tract cannot be carried out, and the most conservative measures compatible with arresting the disease must be instituted.

Resection.—Campbell [3] reported two cases of ureteroheminephrectomy successfully performed on female infants, aged from 6 to 28 months, for ureterohemipyonephrosis. In one case an ectopic ureteral opening was present and at first made the diagnosis difficult. Ectopic ureteral openings, because of urinary leakage, usually result in classify-

2. Collins, D. C.: Congenital Unilateral Renal Agenesia, Proc. Staff Meet. Mayo Clin. **6**:581 (Sept. 30) 1931.

3. Campbell, M. F.: Uretero-Heminephrectomy in Infancy, J. Urol. **26**:433 (Sept.) 1931.

ing the condition as enuresis. One of these cases is the seventh reported of this type in which ureteral ectopy did not result in urinary incontinence. The treatment of hemipyonephrosis is surgical. Infants withstand radical operation on the urinary tract well. Proper preoperative and postoperative care must be taken, since severe acidosis is likely to develop during the first forty-eight hours following operation.

Smith and McKim [4] stated that renal resection is possible, and when indicated in selected cases should include the resection of all diseased tissue. The presence of both kidneys is not absolutely necessary. When the pelvis is opened, urinary fistulas may result; with the lumbar approach and improved technic this is uncommon. The resected kidney will attempt to restore its normal rounded contour and free itself from adjacent adhesions. The remaining portion of the renal parenchyma will attempt to maintain its function, although that portion near the area of resection will become sclerosed due to involvement in scar tissue and the possible occlusion of the vascular supply.

Smith and McKim reported 2 cases in which resection was successfully performed. They emphasized the importance of conserving renal parenchyma and the possibility of conservation instead of complete destruction, after a careful analysis of the data obtained on modern urologic examination.

Ptosis.—Kidd [5] stated that the incidence of movable kidney, as shown by figures taken at random from outpatients at St. Thomas' Hospital by Mackenzie, is 20 among 100 female patients, but only 4 had symptoms; of 515 there were 411 (80 per cent) who did not have symptoms. Of 400 male patients, 4 had movable kidney but only 1 had symptoms. The condition is a disease of adult life.

The support of the kidneys in health is intra-abdominal pressure which is maintained by the tonus of the unstretched muscles of the abdominal wall if persons have well formed chests and the upper part of the abdomen has sufficient cubic space to hold the heart, lungs and supra-umbilical viscera. Adequate support presupposes a well balanced neuromuscular reflex arc. Anchors of the kidneys of healthy persons are the blood vessels in the pedicle of the kidney, the attachments of the peritoneum to the posterior abdominal wall, and the perinephric fibrofatty bands which suspend the kidney from the perinephric fascia. The perinephric fibrofat acts as a suspensory ligament and as a lubricating mechanism which adapts the moving kidney to its fixed surroundings. If the muscles fail, if the thorax grows too narrow, or if there arises

4. Smith, P. G., and McKim, G. F.: The Resection of Localized Areas of Pyo- or Hydronephrosis in the Congenitally Normal Kidney, J. Urol. **25**:203 (Feb.) 1931.

5. Kidd, Frank: Acquired Renal Dystopia or Movable Kidney, J. Urol. **26**: 327 (Sept.) 1931.

sudden trauma, the restrainers of movement or the ligament of the kidney become stretched and thick, and have to take an increasing share in supporting the kidney. Under such circumstances certain symptoms are likely to arise, and a too movable kidney becomes diseased.

The following types of renal dystopia are classified according to their hypothetic cause: 1. The type due to lax abdominal muscles occurs when these muscles have grown slack, as after pregnancy, after the removal of large abdominal tumors, after cutting at operation of the nerves which supply the abdominal wall, or from lack of exercise or improper breathing with the abdomen instead of the thorax, and in states of asthenia. 2. Compression of the hypochondrium stretches the ligaments of the kidney and may be due to rickets or to tight-lacing. 3. The ectopic or unascended kidney of the congenital type is due to failure of the kidney to ascend into its proper position in the loins during fetal life. 4. The narrow flat thorax and the narrow abdomen, good abdominal muscles and a weak nervous system includes two types, one type in which the thorax is wide but flat and the other in which it is flat, narrow and too long. In both types there is a narrow subcostal angle, without space for the supra-umbilical viscera, so that the liver and right kidney and sometimes the other viscera are pushed down into the abdomen.

Various opinions prevail as to the advisability of operation. In certain instances operation is advocated in all cases of movable kidney, with the belief that cure will be effected not only of the renal symptoms but of the mental symptoms which are alleged to be secondary to it. Other physicans neglect the movable kidney and treat only the weakened nervous system, and still others apply certain principles for selecting cases suitable for operation, with the employment of adequate technic. Cases of severe general splanchnoptosis, tuberculosis, chronic cough, disease of the heart and confirmed congenital neurasthenia are excluded as unsuitable for surgical measures. Cases are selected in which there are intermittent attacks of renal drag relieved by recumbency, superadded attacks of pyelitis, a definite history of sudden onset after severe trauma or congenital ectopic kidney. Six months of palliative treatment is tried in most cases. Pyelography determines the suitability of cases for operation. It shows whether there is a fixed twisting, kinking or S-shaped bend of the upper part of the ureter, as a consequence of which there is dilatation and ballooning of the pelvis of the kidney. The need for operation is further indicated if catheterized urine from the ureter shows that the pelvis of the kidney is infected.

Kidd has devised an operation to insure fixing the kidney in the proper position. The salient points of his technic are as follows: A small incision is made, and the muscles are split whenever possible with conservation of the nerves. The incision begins in the costovertebral

angle and extends directly downward until it strikes the edge of the latissimus dorsi muscle, and then it passes anteriorly parallel to the last rib. The perinephritic fat is cleaned off completely, and the renal vessels and upper end of the ureter are denuded, so as to denervate these structures. The fibrous capsule of the kidney is removed from the upper two thirds of the kidney and rolled down over the lower third. Stitches are then put through the rolled portion of the fibrous capsule and brought out through the posterior abdominal wall up above the external arcuate ligament and through the diaphragm above the twelfth rib. The patient remains flat on the back for ten days, and the foot of the bed is elevated on blocks. When the patient arises from bed, a course of abdominal exercise is prescribed.

Tumors.—Prather and Crabtree [6] reviewed 111 cases of the mixed embryonic type of renal tumors among children. Approximately 77.5 per cent of the tumors were of the embryonic adenosarcoma group. Other types in the series were round cell sarcoma, spindle cell sarcoma, myxosarcoma, leiomyo-adenosarcoma and rhabdomyo-adenosarcoma. A moderate number of the adenocarcinomas contained cysts or revealed cystic degeneration. Forty-six and one-tenth per cent of the patients were boys, and 53.9 per cent were girls. The average age was 2.7 years. The relative incidence of tumors of the kidney to tumors in general is 20.4 per cent among children, and 0.5 per cent among adults.

A mass is usually the initial symptom; hematuria and pain are less common. In the 111 cases the first symptom was a mass in 80.1 per cent, hematuria in 14.5 per cent and pain in 5.4 per cent.

The treatment of mixed tumors of the kidney of children is early complete excision, although the absence of symptoms often makes this impossible. Surgical removal of the tumors is not particularly difficult, due to the fact that they are still encapsulated. There is a tendency for the growth to adhere to the peritoneum and large intestine, the latter being displaced mesially. Three methods of approach are employed for removal of these kidneys: lumbar extraperitoneal, median line or rectus transperitoneal and lumbar peritoneal. Of the operative procedures described since 1924, 67 per cent were done by the transperitoneal route and 33 per cent by the lumbar extraperitoneal route. The type of incision does not seem to influence the rate of mortality or end-result. Radium and roentgen rays have been used, but not with satisfactory results.

Wheeler estimated that 80 per cent of tumors of the kidney recur within a year. Warner estimated that the immediate and remote mortality is from 70 to 90 per cent. In the series of 111 cases, 12.3 per

6. Prather, G. C., and Crabtree, E. G.: Kidney Tumors in Children, J. Urol. **25**:589 (June) 1931.

cent of the patients lived two years or longer following operation, 18.4 per cent died within a month of operation and 69.3 per cent of those who survived operation for one month or those who were not operated on, were dead in fifteen months. Although the general outlook in these cases is not favorable, the cures from operation are sufficient to encourage the procedure in the cases in which the growth is not unduly large and is not broken through the capsule.

[ED. NOTE.—The outlook for cure of children with mixed embryonic tumors of the kidney remains relatively poor. Early diagnosis constitutes one of the most difficult phases of the situation. If the tumor could be removed at the beginning of its clinical course, the chance of cure would be fair. It is the uniform opinion that radiotherapy has little to offer in this field.

The frequency of renal tumors during childhood as compared with neoplasms in general during this period is noteworthy and could well be emphasized in campaigns for education concerning carcinoma. The advantage of frequent health examinations of children might be stressed, and renal tumor could be included in the lesions to be looked for by the examining physician.]

Sanford[7] reported a case of carcinoma of both kidneys. Right nephrectomy was done as the only possible means of prolonging life. The upper pole was covered with new growth. A section showed that the kidney was invaded with groups of tumor cells which were arranged in cordlike and alveolar formation. In certain areas the cells were somewhat transitional, as though they had originated from the pelvic mucosa. A diagnosis was made of transitional cell carcinoma of the kidney originating from the pelvis. Three weeks after operation the patient died of uremia. At necropsy, the left kidney was found to be larger than the one removed at operation, and its upper and middle thirds were entirely replaced by a closely packed carcinomatous mass, the gross appearance of which was different from the scattered nodules of tumor in the other kidney.

Orr found that in 7,207 necropsies made in a period of thirty-six years there were 1,046 cases of malignant disease among which were 8 of multiple malignant tumors. In a period of thirty-five years, Junghanns found that in 36,408 necropsies there were 4,192 cases of carcinoma, of which 19 were multiple; 11 patients were men and 8 were women. In none of these cases were both kidneys carcinomatous.

Bilateral primary malignant renal tumors include sarcoma, nephroma and carcinoma. Statistics of their relative frequency vary widely and are confusing. Paul stated that bilateral primary malignant renal tumors are more common among children than among adults, and that

7. Sanford, H. L.: Carcinoma of Both Kidneys, Surg., Gynec. & Obst. **53**:360 (Sept.) 1931.

50 per cent among children are bilateral. Jacobi found 8 cases of bilateral tumor among 41 renal sarcomas. Kuester reported that of 607 malignant renal tumors, 13 were primary bilateral growths. Nicolich reviewed from the literature 19 cases of apparently primary bilateral malignant renal tumors, in 18 of which sarcoma was present on one or both sides. There was no instance of bilateral carcinoma. Kapsammer, in 69 cases of renal tumors, found 3 primary bilateral tumors.

Morelli [8] reported on a histologic study of 6 clear cell renal tumors. Two of these tumors were composed of clear cells arranged in cords, greatly resembling the suprarenal cortex; these were classified as hypernephromas. Three were composed of clear and opaque cells in tubular and papillary formation, and were designated clear cell adenocarcinomas. One tumor was mixed adenocarcinoma and hypernephroma. Morelli reserves the term "hypernephroid" for tumors the histogenesis of which cannot be determined.

Hydronephrosis.—Fister and Smith [9] reported 2 cases of hydronephrosis associated with aberrant vessels, and noted that the first symptom of the condition may appear in infancy. The onset of symptoms of hydronephrosis associated with accessory renal vessels is usually during early adult life.

Opinions vary as to the part these vessels play in the production of hydronephrosis. There are three definite methods by which it may be possible for abnormal vessels to cause urinary stasis leading to dilatation of the renal pelvis: 1. They may act as a mechanical obstruction in the presence of movable kidney or of infection of the kidney and pelvis. 2. They may cause the formation of extra-ureteral adhesions, and in some cases there may be actual ureteral stricture at point of contact. Repeated reinfection of the pelvis of the kidney unquestionably produces periureteritis at the point of crossing of the aberrant vessels, resulting in adhesions and fixation of the ureter. The periureteral adhesions cause narrowing of the ureter which produces urinary retention and hydronephrosis. Continued infection and ureteral irritation eventually will cause actual stricture due to proliferation of connective tissue. 3. According to Quinby, the presence of an anomalous vessel in contact with the ureter is sufficient to cause inhibition of ureteral peristalsis.

The following are some of the symptoms that might suggest the presence of aberrant renal vessels: repeated attacks of pyelitis; absence of calculi; normal urination; normal catheterization of the ureters; intermittent attacks of renal colic; pyelographic evidence of dilatation

8. Morelli, M.: Contributo allo studio dei tumori renali denominati ipernifroidi, Arch. ital. di urol. **7**:303, 1931; abstr., Am. J. Cancer **15**:3024 (Oct.) 1931.

9. Fister, G. M., and Smith, E. H.: Aberrant Renal Vessels in Children, J. Urol. **26**:175 (Aug.) 1931.

of the pelvis of the kidney with a ureteral kink, or narrowing of the upper part of the ureter; a v-shaped retraction of the ureteral orifice, as seen through the cystoscope. A palpable soft tumor is demonstrable in most cases.

Surgical measures are indicated in most cases of hydronephrosis associated with anomalous vessels. Conservative treatment does not afford much relief in advanced cases, and operation in the early cases might often save the kidney. Conservative surgical treatment which removes the obstruction and reestablishes free drainage of urine usually is sufficient in the early cases. Division of vessels, band or adhesions, transplantation of the ureter away from the vessels, nephropexy or plastic operation on the ureteropelvic juncture will relieve the symptoms in some cases. Primary nephrectomy is necessary if much of the kidney is destroyed, and if a serious infection or calculi are present.

[ED. NOTE.—The fact that aberrant renal vessels may produce symptoms in childhood has not been sufficiently appreciated. The clinical picture in this article is excellent. It is generally agreed that noncalculous obstructions at the ureteropelvic juncture should be explored surgically, if conservative treatment by cystoscopic methods does not afford prompt and prolonged relief. Many such obstructive lesions will be found associated with anomalous or aberrant vessels. Division of the vessels and proper attention to drainage of the pelvis into the ureter by pelvioplastic operation, renal fixation, or both, are procedures which, if undertaken early, will save many kidneys that otherwise would become destroyed within a few years.]

Stones.—Herbst [10] stated that recurrence of renal stone after conservative operation for its removal occurs in more than 15 per cent of cases. True recurrence is a new formation of stone after its complete removal. False recurrence is the persistence of stones missed or omitted at the time of operation.

Concentration of the urine is an important factor in the development of urinary lithiasis, since it is more commonly found among persons living in dry, hot zones. In certain areas where the temperature varies from 100 to 130 F., urination is uncommon, since most of the water is eliminated by the skin; the incidence of stone among the natives of this region is almost 100 per cent. Operative trauma, formation of cavity and disturbed drainage with infection are the most significant factors in recurrent renal calculi.

Any disturbance of the renal parenchyma in the removal of stone favors recurrence. Pyelotomy, when surgically possible, is a better surgical procedure than nephrotomy. Cleansing of the pelvis and calices following the removal of stones is important, as sand, small

10. Herbst, R. H.: Recurrent Renal Calculus: Its Cause and Prevention, Am. J. Surg. **12**:58 (April) 1931.

particles of stone, fragments of tissue and blood clots which are not washed away are possible sources of recurrence. All cavities in the kidney should be lavaged with a solution of sodium chloride before the operation is completed. Incrustations should be removed, and if ulcerations are present, they should be curetted. The drainage from a stone-bearing kidney following operation must be adequate. Narrowing at the ureteropelvic juncture is a common factor in the causation of stone, and should be corrected at operation by thorough dilatation or possibly by plastic operation. It should be dilated subsequently if narrowing recurs.

Because of the part infection plays in the production of stone, an attempt should be made to remove all possible foci of infection before any operation on the kidney is undertaken. The infected cavity should be resected if surgically possible. In cases of severe pyonephrosis due to calculi, preoperative drainage and lavage by means of the indwelling ureteral catheter may be means of cleansing an infected organ and of reducing the operative danger and the possibility of recurrence. In any preoperative roentgenologic study, stones are likely to be overlooked because they fail to produce a shadow on a film taken with the kidney in the body, or stones may be superimposed on one another, producing one shadow. In removing a stone, especially with instruments, a small piece or pieces may be broken off and left behind; these promptly cause recurrence. They may be seen on the film but not at operation. Practically all of these conditions may be avoided by fluoroscopy of the exposed kidney before its replacement.

Von Lichtenberg [11] stated that, in rooms in which he performs operations for renal lithiasis, the walls and shades are dark, thus favoring the discovery of stones which may have been left. In the last two years the film method of control has been used to ascertain the situation of stones. A special forceps, shaped like the kidney, is used to draw out the kidney. This instrument has an addition which shows up readily on the plate, and in that way facilitates the recognition of the stone. Although the casettes and forceps may be boiled, the author believes that the asepsis of the operation may be disturbed.

Stones in the lower part of the ureter are removed by operating in at least 30 per cent of his cases. Early surgical intervention is preferable in a certain percentage of cases.

Newcomb and Ranganathan [12] analyzed 226 urinary calculi. Seventy-three of these were so small that microscopic methods were necessary.

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11. von Lichtenberg, Alexander, in discussion on Kidney and Ureteral Stones, J. Urol. **25**:181 (Feb.) 1931.

12. Newcomb, Clive; and Ranganathan, S.: The Composition of Urinary Calculi, Indian J. M. Research **17**:1037 (April) 1930; abstr., Ztschr. f. urol. Chir. **31**:60 (Dec. 18) 1930.

All but 5 of the stones were from the bladder. The average composition was 24.9 per cent calcium oxalate; 7.4 per cent calcium phosphate; 6.9 per cent magnesium ammonium phosphate; 6.2 per cent protein; 49.7 per cent uric acid, and 4.9 per cent various other salts. The latter consist chiefly of carbonates and insoluble ash, and sulphur was found in traces in some stones. Only 26 (11.8 per cent) were pure or uniform stones. The remainder were mixed; the most common combination was urates and oxalates. Urates were found in 187 stones (84.6 per cent), and in 120 cases phosphates were found. The vesical stones were the most mixed in composition, the majority containing a combination of urates or uric acid with oxalates. Of the pure stones, uric acid stones were most frequently found (6.8 per cent). Urates were found in 53 per cent of the stones, oxalates in 17 per cent and phosphates in 12 per cent.

The small number of renal stones, 5, is indicative that such cases are not common in India; the converse is true in America and Europe.

Price and Jacobs [13] recorded a case of primary squamous carcinoma in a hydronephrotic kidney with renal stones.

The patient, a laborer, aged 54 years, complained of pain in the lumbar region. A large mass could be felt in the left side of the abdomen, extending from under the left costal margin down to the iliac region. The urine contained albumin, blood and pus. Roentgenograms disclosed shadows of at least 11 calculi of varying dimensions in an area extending from below the iliac crest upward to the level of the second lumbar vertebra. At operation, the kidney was exposed through a curved lumbar extraperitoneal incision. The organ was large and extremely difficult to deliver, but this was successfully accomplished after resection of the twelfth rib. Following division of the ureter and ligature of the pedicle, the kidney was removed without further trouble.

The removed kidney measured about 18 cm. from pole to pole and about 11 cm. in its greatest transverse diameter. The surface of the organ was coarsely lobulated, and it was obviously cystic and contained fluid. On hemisection the parenchyma was found to be practically obliterated, being reduced to a thin shell of tissue not more than 1 mm. thick. In the interior of the organ were large cystic spaces, separated from each other by attenuated renal substance and containing fluid. The region normally occupied by the pyramids contained a quantity of dense, partly embedded fibrofatty tissue, in which were a number of large irregular calculi. At the lower pole the dilated calix was partly occupied by a cauliflower-like tumor about 5 cm. in diameter. In the center of the tumor were two irregular spaces occupied by a number of small faceted calculi. Distributed irregularly in the fibrofatty tissue of

13. Price, L. W., and Jacobs, Arthur: Renal Calculi with Squamous Carcinoma in a Hydronephrotic Kidney, Brit. J. Surg. **28**:590 (April) 1931.

the central portions of the organ, but occupying chiefly the lower half, were several large calculi. Sections of tissue from the tumor occupying the lower pole of the kidney showed the structure of a squamous cell carcinoma. This probably arose in the epithelium of the lower calix, which had undergone squamous metaplasia, as the transitional epithelium in this region showed hyperplasia and in places a definite tendency to assume squamous characteristics.

[ED. NOTE.—There are two types of squamous cell tumors arising in the renal pelvis; in the first type the parenchyma is invaded early, the kidney is solid and compact, and the parenchymal tissue becomes completely replaced by carcinoma and irregular masses of fibrosis; in the second type the growth is confined to the pelvis, the kidney is extremely large and hydronephrotic with pressure atrophy of most of the renal tissue. It is possible that in certain cases the development of the carcinoma of the pelvis may precede the formation of stones. Hallé maintained that the metaplasia does not result from irritation of the stone, but that epidermization and calculi both result from the same chronic inflammation. The stones in the pelvis may be extremely large, and of the staghorn earthy-phosphate type. These tumors are comparatively symptomless. When obstruction occurs, it is from gradual slow occlusion and is almost painless. In contrast to papillary tumors, the squamous cell carcinoma rarely bleeds. The mortality after operation, usually nephrectomy, is high, as the patients die shortly after the operation from local recurrences or metastatic growths.]

URETER

Stricture.—Campbell [14] reported 15 cases of congenital bilateral stricture at the ureterovesical juncture. The patients were infants and children; the condition of 11 was discovered at urologic examination, and of 4 at necropsy. The ages of the 11 patients varied from 2 months to 11 years, and of the other 4 from stillbirth to 6 months.

Sclerosis, increase in localized connective tissue, scarring and inflammation, or only narrowing of the lumen of the ureter without fibrosis may be found. The late results of urinary backpressure with infection are found in the elongated, angulated, tortuous, atonic scarred ureters and in the thinned sclerosed and infiltrated renal tissue. The symptoms are due to infection and to loss of renal function, pyuria being the outstanding objective symptom. Patients usually are treated for chronic pyelitis because of persistent pyuria. In Campbell's cases, the colon bacillus was the predominant invading organism. Gastro-intestinal

14. Campbell, M. F.: Congenital Bilateral Uretero-Vesical Junction Stricture in Infants and Children, J. Urol. **26**:529 (Oct.) 1931.

upsets, fever of low grade, anemia, malaise, loss of weight or failure to gain weight are common symptoms. Pain is rare, and if present usually is localized to the loin and is due to hydronephrotic distention. Inflammation of the secondary vesical outlet causes frequency of urination, burning, dysuria or hematuria. Persistent pyuria is the usual indication for complete urologic examination; it was the only cause for investigation in Campbell's cases.

Two characteristic observations may be made: (1) It may be impossible to insert a catheter into the ureter; sometimes not until the second or third examination can even a number 4 French filiform tip be passed; on withdrawing the catheter it is so firmly grasped by the stricture that the wall of the bladder may be pulled with it, and (2) the pyelogram shows a dilated ureter beginning in the region of the stricture and terminating in a hydronephrotic renal pelvis. Following retrograde pyelography, the catheter should be left in position until the injected material has been withdrawn. In this series of cases the combination of catheter grasping, hydronephrotic drip and widely dilated upper tract was found, making the diagnosis of stricture unquestionable.

The object of treatment is to eliminate the obstruction. In 6 of the cases dilation by catheter was carried out. It is usually difficult to pass even a number 4 French catheter at first; after this has been done, two, three or four catheters of the same size may be passed side by side. This technic is required by the small urethral caliber. The procedure is done every ten days at first; then dilation may be done once a month or once in three months according to the rate and degree of recontraction. If satisfactory dilatation is not obtained by cystoscopic methods, transvesical ureteral meatotomy and section of the stricture may be done. Catheters are passed up the ureters as guides. Through the open bladder the stricture is divided against the inlying catheter and cut through to it. Beginning at the ureteral meatus the incision is made upward from 1 to 1.5 cm. Cutting the dense tissues gives the sensation of cutting cartilage. The incised stricture is then widely dilated with a number 14, 16 or 18 French sound, and a whistle tip of soft rubber catheter is inserted from 8 to 12 cm. in the ureter, where it is anchored for a week. These catheters, one from each side, are brought out through the open bladder, and the drainage material is collected. If the patient is extremely ill, with low renal function, preliminary drainage with bilateral ureterostomy is indicated.

Although operative treatment may not always afford complete cure, it offers more than any other method. Medical treatment alone is not adequate. Continued backpressure, renal destruction and uremia produce a fatal outcome.

Hurst and Gaymer-Jones [15] stated that the pathogenesis of enormous dilatation of the ureters without evidence of obstruction has been a controversial subject. It has been attributed to congenital muscular insufficiency, inflammatory atony or to neuromuscular dysfunction. They reported a case of a woman, aged 33, with left megalo-ureter without stenosis of the lower part of the ureter, and advanced the hypothesis that these dilatations are caused by an absence of relaxation of the ureterovesical sphincter. The mechanism of dilatation is compared to that which obtains in cardiospasm and megacolon. It was formerly supposed that the esophageal dilatation and hypertrophy in the former condition was caused by spasm at the juncture of the esophagus and cardia of the stomach, but Hurst observed that it is caused by achalasia or failure of relaxation of the sphincter as the result of disturbance of the intrinsic supply to the nerves. The inert sphincter acts as an obstruction, and excessive propulsive efforts produce hypertrophy and dilatation of the esophagus. The same mechanism applies in cases of megacolon, in which the hypertrophy and dilatation of the colon are caused by achalasia of the anal sphincter of the pelvirectal sphincter.

From the authors' observations, megalo-ureter without evidence of organic obstruction is attributed to degenerative changes in the nerve supply in the pars intramuralis of the ureter. This is the result of inflammation in the mucosa which spreads to the muscularis producing degeneration of nerves which progresses long after the primary inflammation of the mucosa has disappeared. On cystoscopic examination the ureteral orifice is relaxed and patent, and there is no obstruction to the passage of a catheter or "hang" on withdrawal of the bulb.

Moore [16] reported on the clinical and roentgenographic study of approximately 75 cases of ureteral meatotomy performed over a period of seven years, from which he made the following conclusions:

The operation is comparatively minor but technical. The high-frequency meatome, when properly applied, is effectual and safe. It is possible to continue work higher on the ureter at the same sitting without any alarming complications. Stricture does not follow the operation. In a number of cases the ureteral opening was sufficiently large to pass number 7 and 9 catheters, after which there was temporary relief. More permanent relief followed wide incision of the opening. Symptoms or signs of regurgitation were not observed at any time after the operation.

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15. Hurst, A. F., and Gaymer-Jones, J.: A Case of Megalo-Ureter Due to Achalasia of the Uretero-Vesical Sphincter, Brit. J. Urol. **3**:43 (March) 1931.

16. Moore, N. S.: Ureteral Meatotomy: A Clinical Evaluation, J. Urol. **26**: 519 (Oct.) 1931.

Diverticulum.—Bugbee [17] stated that diverticulum of the ureter is rarely seen. It has been produced experimentally. In 4 cases it was found at necropsy, and 7 clinical cases have been reported, to which the author adds 3. Three possibilities as to the etiology of ureteral diverticula are: (1) secondary budding of the metanephric anlage, (2) compensatory structure following congenital stenosis of the ureter and (3) acquired structure occurring late following an acquired ureteral stricture.

In 9 cases of diverticulum of the lower part of the ureter a ureteral catheter was obstructed in its passage, and in all except 2 cases roentgenograms taken afterward showed the catheter coiled in the diverticulum. The diagnosis was verified by a ureterogram in each case. Congenital diverticulum of the ureter may be present and not lead to investigation until later in life when symptoms due to infection or to the formation of calculus arise.

The treatment for diverticulum of the ureter usually is surgical, as in 8 of the 10 reported cases. Two patients were relieved by dilation of the ureter and intra-ureteral manipulation, to establish freer drainage of the diverticulum.

Infection.—Dourmashkin [18] stated that empyema of the ureter does not occur except in the presence of a preexisting diseased state. The local pathologic changes are marked periureteritis, dilatation of the ureter and firm adhesions of the stump to the surrounding tissues. Besides pus, calcified material was found in one of the cases in which operation was performed by Hyman.

Dourmashkin reported in detail 4 cases of empyema of the ureter. There were no symptoms of irritability of the bladder, and the voided urine, ordinarily purulent, would in some cases be clear temporarily because of closure of the sac. Pus exuding from the ureteral orifice on the nephrectomized side, as seen through the cystoscope, does not necessarily indicate the presence of a dilated ureter filled with pus. In one case a diagnosis of empyema of the ureter was made because of thick pus escaping from the orifice of the ureteral stump. The presence of pus was due to a stone just below the ureteropelvic juncture which was not removed at the time of nephrectomy.

Clinical cure was affected in one case by cystoscopic manipulations. The orifice was enlarged by a fulgurating spark and the sac drained and irrigated with antiseptic solutions. Five years later, examination revealed that the urine was normal and there were no other symptoms.

17. Bugbee, H. G.: Diverticulum of the Ureter: A Report of Three Cases, J. Urol. **26**:215 (Aug.) 1931.

18. Dourmashkin, R. L.: Empyema of the Ureteral Stump, J. Urol. **26**:553 (Oct.) 1931.

In general, the absence of vesical or other local symptoms which do not indicate a tendency of extension of the infection into the remaining kidney should be left alone.

Draper, Darley and Harvey [19] observed that intramuscular injections of pituitary extract and pitressin reduce the size and density of the pelvic and ureteral shadow, as shown by intravenous urography. The change in pelvic and ureteral visualization is more pronounced as the dosage is increased. With the maximal dose (15 minims) marked diminution in the size and density of the shadows occurs from three to seven minutes after the injection. Since neither pituitary extract nor pitressin when injected intramuscularly produces antidiuresis in the face of diuresis previously induced by iopax administered intravenously, it is concluded that the shadow diminishes due to accelerated drainage caused by active ureteral and pelvic peristalsis and not to antidiuresis.

In a clinical case of pyelitis with bilateral hydronephrosis and hydroureter, marked relief of pain followed the exhibition of solution of pituitary, which proved more alleviating than ⅙ grain (11 mg.) of morphine. It is possible that the clinical improvement noted was due in part to certain changes in the composition of the urine, as brought about by administration of pituitary extract.

Tumor.—Frazer [20] reported a case of primary carcinoma of the ureter, which was under observation for four and half years.

Pathologically, ureteral neoplasms are similar to those found in the pelvis of the kidney and the bladder. The types that have been reported are papilloma, benign and malignant, fibroma, papillary carcinoma, squamous cell epithelioma and sarcoma. Primary carcinoma of the ureter is rare. Its presence is suspected in cases of painless hematuria when bloody urine can be seen coming from the ureteral meatus and when the more common conditions are excluded. Varying degrees of obstruction to the lumen cause secondary changes in the kidney. Nephrectomy and complete ureterectomy, combined or as a two-step procedure, is the only adequate treatment. Early diagnosis and radical surgical measures should lower the mortality in these cases, as in cases of operable carcinoma in other parts of the body.

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19. Draper, W. B.; Darley, Ward; and Harvey, J. L.: The Effect of Pituitary Extract Upon the Tonus of the Human Pelvis and Ureter and Its Possible Application in the Therapeutics of Pyelitis and Related Conditions, J. Urol. **26**:1 (July) 1931.

20. Frazer, E. B.: Primary Carcinoma of the Ureter, Bull. Mobile City Hosp. July, 1931.

(To be Concluded)